Universität Zürich[UZH]

Omega-3 and Cognition: The Influence of Omega-3 Fatty Acids on Cognitive Functions in Youths

Thesis (cumulative thesis)
presented to the Faculty of Arts and Social Sciences of the University of Zurich
for the degree of Doctor of Philosophy

by Sophie Emery

Accepted in the fall semester 2020
on the recommendation of the doctoral committee:

Prof. Dr. Lutz Jäncke (main supervisor)
Prof. Dr. Renate Drechsler

Zurich, 2020

Table of Contents

Summary

Omega-3 fatty acids are vital for brain development and have been associated with positive health outcomes. However, there is yet no clear understanding about the cognitive effects of supplementation in youths. Furthermore, a research deficit exists concerning associations of omega-3 fatty acids and cognitive functioning in psychiatric disorders, especially in youths. This thesis broadens current knowledge about the aforementioned issues. A meta-analysis dealing with the effects of omega-3 fatty acid supplementation in youths revealed no overall beneficial effect of supplementation, however small beneficial effects were found for eicosapentaenoic acid (EPA)-rich but not docosahexaeonic acid (DHA)-rich formulations. A tendency towards stronger effects in clinical rather than healthy populations presented. The second study investigated associations between blood omega-3 fatty acid status and verbal memory performance in depressed youths. Similar results to the ones reported in the meta-analysis presented, where EPA but not DHA status was positively associated with short-term verbal memory performance. Both studies hence suggested that EPA rather than DHA might be positively related to cognitive test performance in youths. They also both suggested associations in clinical populations. Future studies should further evaluate potential cognitive supplementation effects of EPA and DHA separately, in order to establish specific recommendations for supplementation in youths.

Zusammenfassung

Omega-3 Fettsäuren sind für die Gehirnentwicklung unerlässlich und werden mit positiven Gesundheitsfolgen in Verbindung gebracht. Der genaue Einfluss von Omega-3 Supplementierung auf die Kognition bei Kindern und Jugendlichen ist jedoch zum heutigen Zeitpunkt noch nicht abschliessend untersucht. Ausserdem besteht eine Forschungslücke, was den Zusammenhang zwischen Omega-3 Fettsäuren und kognitiven Funktionen bei psychischen Erkrankungen betrifft, dies vor allem bei Kindern und Jugendlichen. Die vorliegende Dissertation erweitert den aktuellen Wissensstand zu dieser Thematik. Eine Meta-Analyse zum Einfluss von Omega-3 Supplementierung auf die kognitive Testleistung von Kindern und Jugendlichen konnte keinen generellen positiven Effekt von Omega-3 Supplementierung feststellen, hingegen konnten kleine positive Effekte von Eicosapentaensäure (EPA)-reichen, nicht aber von Docosahexaensäure (DHA)-reichen Präparaten festgestellt werden. Es konnte eine Tendenz zu positiven Effekten in klinischen Stichproben im Vergleich zu gesunden Stichproben aufgezeigt werden. Die zweite Studie befasste sich mit dem Zusammenhang zwischen dem Omega-3 Status im Blut und verbaler Gedächtnisleistung bei depressiven Kindern und Jugendlichen. Hier gingen die Ergebnisse in dieselbe Richtung, da für den EPA Status, nicht aber für den DHA Status ein positiver Zusammenhang mit der verbalen Gedächtnisleistung gefunden werden konnte. Beide Studien weisen somit darauf hin, dass eher EPA und nicht DHA mit der kognitiven Testleistung bei Kindern und Jugendlichen in Verbindung steht. Ausserdem weisen beiden Studien auf Zusammenhänge in klinischen Stichproben hin. Zukünftige Studien sollten Supplementierungseffekte von EPA und DHA gesondert untersuchen, um spezifische Supplementierungsempfehlungen für Kinder und Jugendliche entwickeln zu können.

List of Figures

List of Tables

List of Abbreviations

AA	arachidonic acid
ADHD	Attention Deficit Hyperactivity Disorder
ALA	alpha-linolenic acid
ANCOVA	univariate analyses of covariance
ANT	Amsterdam Neuropsychological Tasks
AVLT	Auditory Verbal Learning Test
BDNF	brain-derived neurotrophic factor
BMI	body mass index
CDR	Cognitive Drug Research Battery
CDRS-R	Children's Depression Rating Scale revised
CPT-IP	The Continuous Performance Test, Identical Pairs Version
CRP	C-reactive protein
CVLT	California Verbal Learning Test
DALY	disability-adjusted life years
DHA	docosahexaeonic acid
DPA n-3	docosapentaenoic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ENI	Evaluación Neuropsicológica Infantil
EPA	eicosapentaenoic acid
FFQ	food frequency questionnaire
FIQ	full scale IQ
FO	fish oil
GIX	global intelligence index
HAWIK-IV	Hamburg-Wechsler-Intelligenztest für Kinder
HPA axis	hypothalamic-pituitary-adrenal axis
HVLT-R	Hopkins Verbal Learning Test–Revised
ICD-10	International Classification of Diseases, Tenth Revision
IL	interleukin
IQ	intelligence quotient
KABC-II	Kaufman Assessment Battery for Children – Second Edition
(Ki)TAP	(Kinder)-Testbatterie zur Aufmerksamkeitsprüfung
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
LA	linoleic acid
LC-PUFAs	long-chain polyunsaturated fatty acids
LTD	long-term depression
LTP	long-term potentiation
M	mean

MANCOVA	multivariate analyses of covariance
MCI	mild cognitive impairment
MDD	major depressive disorders
MDI	mental development index
NAPLAN	National Assessment Program - Literacy and Numeracy
NIX	nonverbal intelligence index
N-3	omega-3
N-6	omega-6
N-9	omega-9
PFC	prefrontal cortex
PIQ	performance intelligence quotient
pMDD	pediatric major depressive disorder
PUFAs	polyunsaturated fatty acids
Q-Q plot	Quantile-Quantile plot
RAVLT	Rey Auditory Verbal Learning Test
RBC	red blood cell
RCT	randomized controlled trial
RIAS	Reynolds Intellectual Assessment Scales and Screening
SC-PUFAs	short-chain polyunsaturated fatty acids
SD	standard deviation
SE	standard error
SMD	standardized mead difference
TEA-ch	Test of Everyday Attention for Children
TMT A/B	Trail Making Test Part A/B
TNF	tumour necrosis factor
TOVA	Test of Variables of Attention
VIQ	verbal intelligence quotient
VIX	verbal intelligence index
VLMT	Verbaler Lern- und Merkfähigkeitstest
WHO	world health organization
WIAT-II	Wechsler Individual Achievement Test – Second Edition
WISC-III/IV	Wechsler Intelligence Scale for Children, Third/Fourth Edition
WMTB-C	Working Memory Test Battery for Children
WORD	Wechsler Objective Reading Dimensions
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence
WRAT4	Wide Range Achievement Test, Fourth Edition
YLD	years lived with disability

1 General Introduction

Nutritional patterns have changed dramatically since the industrial revolution, with main health concerns related to the dramatic increase in intake of omega-6 fatty acids compared to omega-3 fatty acids (Simopoulos, 2002, 2011a). Among other adverse health outcomes discussed, these changes have been associated with potential adverse outcomes concerning cognitive development and functioning (Simopoulos, 2011a, 2011b). Because omega-3 fatty acids are part of the lipid bilayer of the brain and have been shown to be involved in many core elements of cognitive development (J. Baumgartner, 2016; Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008; Lauritzen et al., 2016; Sun et al., 2018), concerns have arisen related to a potential deficiency of omega-3 fatty acids. Consequently, research investigating the association between omega-3 fatty acids and cognitive development and potential beneficial effects of omega-3 fatty acid supplementation on cognitive functioning has increased.

Cognitive functions like memory and attention influence all aspects of everyday functioning and deficits can hence have detrimental effects on all aspects of life. Because the human brain develops until the age of about 25 (Arain et al., 2013; S. B. Johnson, Blum, & Giedd, 2009; Sowell et al., 2003; Thompson et al., 2000), youths constitute an especially vulnerable subgroup when it comes to the disruption of cognitive development and functioning. In some psychiatric diseases, for example, cognitive complaints constitute key symptoms, which might have detrimental effects for later life in this vulnerable population. In depressed youths, cognitive complaints have been negatively associated with vocational, social and independent functioning and educational attainment (Fletcher, 2008; Morey-Nase et al., 2019). Improving deficits concerning cognitive functioning or even improving healthy cognition by means of omega-3 supplementation has hence been discussed within several research fields. Especially in young and clinical populations, improving cognitive deficits might prove essential in order to improve quality of life. This dissertation introduces omega-3 fatty acids as a potential natural nutritional supplement for improvement of cognitive test performance. The current dissertation will tackle the following general research questions: 1) Does previous research suggest a beneficial effect of omega-3 fatty acid supplementation on cognitive test performance in children and adolescents? 2) If so, are there differences depending on the type of omega-3 fatty acid ingested? 3) Do specific populations, like for example clinical subgroups compared to healthy subgroups, benefit differently from supplementation? 4) Is the omega-3 blood status related to cognitive test performance in children and adolescents with major depressive disorder? 5) If so, are there differences concerning the type of omega-3 fatty acid ingested? The following chapters give

an introductory overview over basic concepts and current research related to these questions. More specific research questions related to the research papers included in this dissertation, are given at the end of the respective introductory sections.

This dissertation was written as part of "The Omega-3-pMDD trial", a multi-center placebo-controlled trial investigating the efficacy of omega-3 fatty acid supplementation in depressed youths aged 8-17 years. The trial is funded by the Swiss National Foundation. The clinical trial has been registered on www.ClinicalTrials.gov protocol no. NCT03167307.

1.1 Omega-3 fatty acids

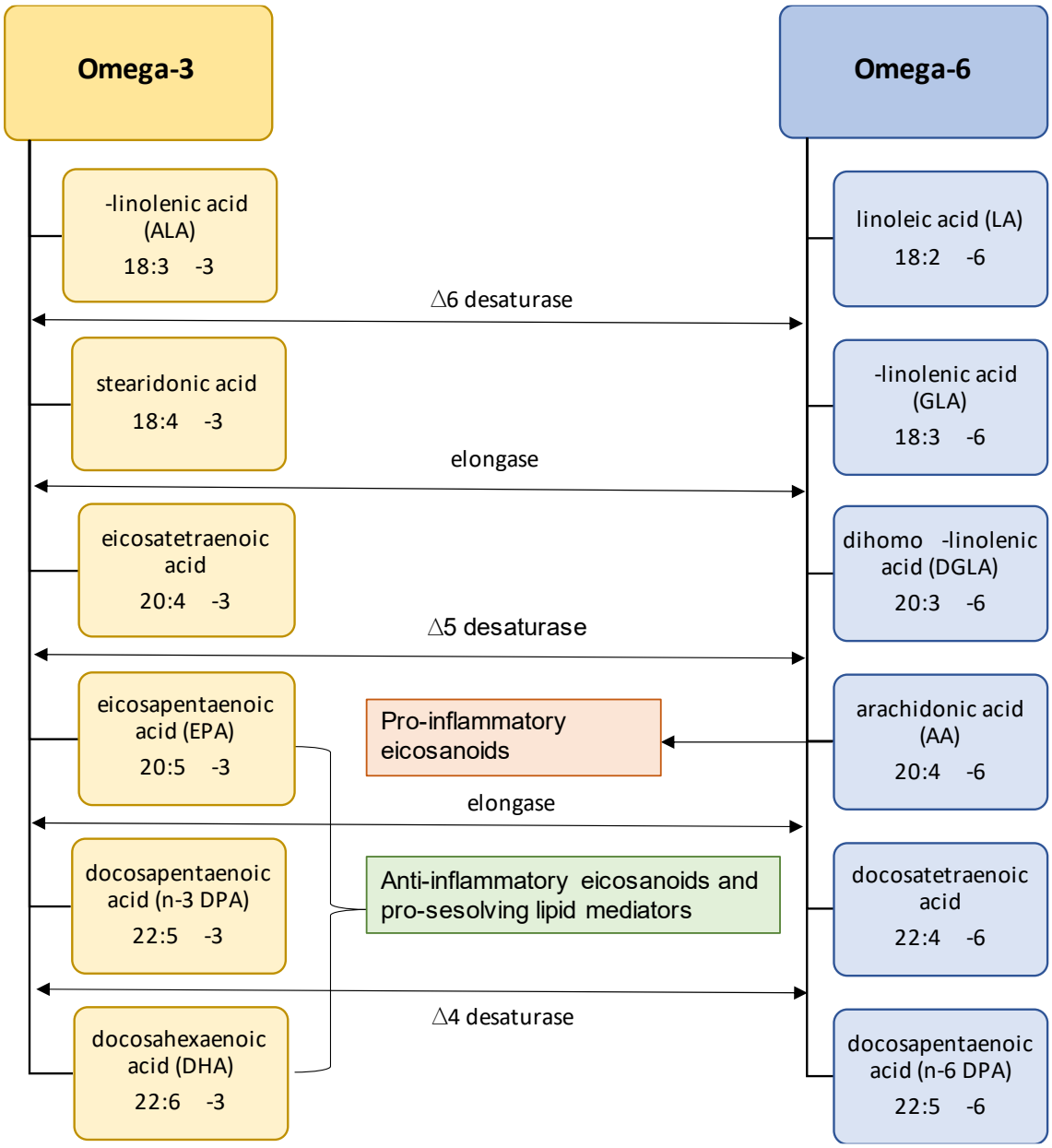
Omega-3 fatty acids are one of two classes of polyunsaturated fatty acids (PUFAs) that play an essential role in human nutrition (Jones & Rideout, 2012) and are considered to influence numerous health outcomes (Simopoulos, 2002, 2008). In this chapter, omega-3 PUFAs are introduced concerning their chemical structure and synthesis, potential health outcomes and methods of measurement.

1.1.1 Chemistry

PUFAs are fatty acids that contain more than one carbon double bond (Jones & Rideout, 2012). They can be classified into two groups, namely short-chain polyunsaturated fatty acids (SC-PUFAs) and long-chain polyunsaturated fatty acids (LC-PUFA), based on the number of carbon atoms in their backbone (Buckley et al., 2017; Jones & Rideout, 2012). Furthermore, they can also be grouped into omega-3 (n-3) and omega-6 (n-6) fatty acids, based on the location of the carbon double bond in relation to the terminal methyl group (Jones & Rideout, 2012). The precursors of long-chain n-3 PUFAs and long-chain n-6 PUFAs are alpha-linolenic acid (ALA) and linoleic acid (LA) respectively. Both are essential fatty acids, which means that the human body is unable to synthesize these fatty acids and hence relies on the intake through nutrition (J. Baumgartner, 2016; Bazinet & Layé, 2014; Simopoulos, 2011a; Weiser, Butt, & Mohajeri, 2016). ALA can be found in a number of seeds and their derived oils like walnuts, chia seeds or linseeds and LA is abundantly found in for example safflower and corn (Jones & Rideout, 2012). In the liver, ALA and LA are desaturated by adding a carbon bond, resulting in the synthesis of LC-PUFAs (Bazinet & Layé, 2014). However, this process is considered not to be very efficient (approx. < 5%) (Brenna, 2002). The enzyme Δ6 desaturase plays an important role in the desaturation process and is hence considered to limit the rate of desaturation (Bazinet

& Layé, 2014). It is currently believed that n-3 and n-6 PUFAs compete for elongation because they share the same enzymes responsible for desaturation (Bazinet & Layé, 2014). Also, ingestion of n-6 PUFAs is an important determinant of n-3 PUFA incorporation into membranes, where high levels of n-6 PUFAs inhibit n-3 PUFA incorporation (Simopoulos, 2008). Furthermore, animal studies have suggested that n-3 PUFA deficiency is often compensated with the nearest equivalent n-6 PUFAs (Carrié, Clément, De Javel, Francès, & Bourre, 2000; Neuringer, Connor, Lin, Barstad, & Luck, 1986). The nutritionally most important LC-PUFAs are eicosapentaenoic acid (EPA) and docosahexaeonic acid (DHA) which are n-3 PUFAs, and arachidonic acid (AA), which is an n-6 PUFA (Layé, Nadjar, Joffre, & Bazinet, 2018). EPA and DHA can mostly be found in fatty fish, whereas AA is abundantly found in all sorts of meat (J. Baumgartner, 2016). The synthesis cascade starting from the parent fatty acids ALA and LA is depicted in detail in Figure 1.

Figure 1
Synthesis cascade of n-3 and n-6 PUFAs.



Note. n-3 generally have anti-inflammatory properties, whereas n-6 promote inflammation. Conversely, γ-linolenic acid (GLA) has been shown to attenuate inflammatory processes (Sergeant, Rahbar, & Chilton, 2016).

1.1.2 Health benefits

Since the industrial revolution, PUFA intake in Western populations has shifted dramatically, from a balanced n-6:n-3 PUFA ratio to a ratio of about 15-25:1 (Simopoulos, 2011a). Because these developments have taken place in evolutionarily very short periods of time, they have not

been accompanied by balancing genetic changes, leading to inequalities between human genetic constitution and nutritional habits (Grosso, Galvano, et al., 2014). These dramatic nutritional changes have been linked to several diseases of civilization like cancer and cardiovascular diseases but also psychiatric disorders (Simopoulos, 2011). Lower n-3 PUFA intake has for example been associated with an increased risk of developing depression (Appleton, Rogers, & Ness, 2010). On the other hand, n-3 PUFA consumption has been associated with a decreased risk of, and beneficial effects on several diseases like cancer (Anderson & Ma, 2009; S. Lee et al., 2018; Vaughan, Hassing, & Lewandowski, 2013), diabetes (Anderson & Ma, 2009; Natto, Yaghmoor, Alshaeri, & Van Dyke, 2019) and cardiovascular diseases (Anderson & Ma, 2009; Din, Newby, & Flapan, 2004; J. H. Lee, O'Keefe, Lavie, & Harris, 2009; Lovegrove et al., 2004; Massaro, Scoditti, Carluccio, & De Caterina, 2008; Natto et al., 2019; Psota, Gebauer, & Kris-Etherton, 2006). However, a recent Cochrane review now concluded that, against common belief, n-3 PUFA consumption had little or no effect on cardiovascular health (Abdelhamid et al., 2018). In general, meta-analytic evidence concerning n-3 PUFA health benefits has proven rather heterogenous (Fang, Li, Qian, Zeng, & Ye, 2017; Hanson et al., 2020). The association between dietary changes and the development of diseases of civilization is thought to mainly be driven by the proinflammatory and pro-thrombotic properties of n-6 PUFAs (Simopoulos, 2008). n-3 PUFAs, on the other hand, have anti-inflammatory properties, as they give rise to important anti-inflammatory and pro-resolving mediators, reducing inflammation (Bazinet & Layé, 2014; Layé et al., 2018; K. Li, Huang, Zheng, Wu, & Li, 2014). Consequently, higher n-3 PUFA intake has also been associated with a decreased risk of developing certain neurological disorders that have been shown to be closely related to inflammatory processes (e.g. Alzheimer's disease) (Layé, 2010). Because a number of studies have postulated an inverse relationship between DHA intake and the risk of developing certain neurological disorders like Alzheimer's disease (AD) (Cole & Frautschy, 2010), the anti-inflammatory properties of n-3 PUFA have been thought to benefit brain function and cognition (Layé, 2010). This might also apply to other psychiatric diseases like major depressive disorder (MDD), where inflammation has been discussed to play a significant role (A. H. Miller & Raison, 2016) and cognitive complaints are a main symptom. In depression, emotional symptoms as well as symptoms related to cognition might hence benefit from n-3 PUFA supplementation (Layé, 2010). The role of n-3 PUFAs in relation to MDD will be discussed in detail in chapter 1.6. Because n-3 PUFAs are part of the cell membrane and are amply found within the human brain, they have also been thought to impact cognitive developmental processes (Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008; Lauritzen & Carlson, 2011). The

role of n-3 PUFAs in the brain and potential implications for cognitive development and functioning will be discussed in depth in chapter 1.2.

1.1.3 Measuring n-3 PUFA levels

Specific food frequency questionnaires (FFQ) have been developed in order to measure n-3 PUFA intake (Herter-Aeberli et al., 2019; Rahmawaty, Charlton, Lyons-Wall, & Meyer, 2017; Sublette, Segal-Isaacson, et al., 2011). Along with common shortcomings of self-report questionnaire procedures such as response bias, lack of motivation or comprehension difficulties, the lack of an individual's memory concerning his or her daily consumption of different kinds of foods, constitutes a serious drawback. Monitoring and remembering one's own food consumption can be difficult and self-report questionnaire results are hence unlikely to validly measure n-3 PUFA intake, especially in younger individuals. Furthermore, results are calculated using separate details concerning nutritional components for each food. This constitutes a further drawback, as the n-3 PUFA content, for example in fish, has changed significantly over the past few years and nutritional information might hence be outdated (von Schacky, 2016). Even more, the large inter-individual differences in n-3 PUFA absorption rates may further bias results (Köhler, Bittner, Löw, & Von Schacky, 2010). Hence, n-3 PUFA supplementation trials often rely on n-3 PUFA levels measured in human blood. Here, the omega-3 index is often used to measure n-3 PUFA levels in erythrocytes. This index reflects the sum of total EPA and DHA levels expressed as a percentage of total fatty acids measured in red blood cell membranes (Harris, von Schacky, & Park, 2013). Current evidence suggests that this index should ideally lie between 8-11% (Von Schacky, 2015), with a minimum of 2% and a maximum of 20% (von Schacky, 2019b). In Western populations where fish intake is rather low, the omega-3 index has been found to typically lie between 3-5% (Harris, 2010). Although determining this biomarker is a standardized procedure and can be validly used to, for example, measure compliance with study medication in randomized controlled trials (RCTs), little is known about the actual absorption and utilization of n-3 PUFAs in the brain. Also, our current understanding of the influence of genes, the microbiome or interactions with other substances and nutrients remains rather poor. Even more, the influence of the nutritional status on specific health benefits is still being investigated.

1.2 n-3 PUFAs in the developing brain and their influence on cognition

In this chapter, the role of n-3 PUFAs in the developing brain is delineated. Current knowledge about the effects of n-3 PUFA supplementation on cognitive functioning in youths is explored in the second part of this chapter and the last part deals with research on the associations between n-3 PUFAs and memory in particular.

1.2.1 n-3 PUFAs and neurodevelopment

In the brain, lipids account for about 50-60% of its dry weight, of which about 35% are LC-PUFAs (Hamilton, Hillard, Spector, & Watkins, 2007). LC-PUFAs are very important for nerve cell structure and function (for a review see Bazinet & Layé, 2014). Especially DHA and AA are abundantly found in the human brain, with DHA accounting for about 10-20% of total brain fatty acids (Bazinet & Layé, 2014; McNamara & Carlson, 2006; Weiser et al., 2016). Within the brain, DHA and AA are unequally distributed, with larger amounts of DHA in gray matter and larger amounts of AA in white matter (Bazinet & Layé, 2014; Weiser et al., 2016). EPA on the other hand only makes up for < 1% of total brain fatty acids (Bazinet & Layé, 2014; McNamara & Carlson, 2006; Weiser et al., 2016). EPA concentration is around 200-500 times lower than DHA concentration although EPA and DHA both enter the brain at a very similar rate (Bazinet & Layé, 2014). This is mainly a result of the fast catabolization of EPA to docosapentaenoic acid (DPA n-3) and DHA (Bazinet & Layé, 2014).

PUFAs have diverse effects on various bodily systems. The bioactive roles of EPA and DHA and their bioactive mediators have been extensively reviewed in Dyall (2015), Layé et al. (2018) and Weiser et al. (2016). Most importantly, PUFAs form an essential part of the lipid bilayer of the cytoplasmic membrane and hence have a large impact on membrane fluidity and other membrane dynamics (for a review see Gawrisch, Eldho, & Holte, 2003; Salem, Litman, Kim, & Gawrisch, 2001; Shaikh & Teague, 2012). Changes in the fluidity of the membrane lead to alterations in the rotation and diffusion of proteins and other molecules. Transmission, for example, is facilitated in more fluid membranes (Weiser et al., 2016). These alterations in turn highly affect molecule functioning which might have large implications in neuropsychiatric disorders (Guixà-González et al., 2016). An important underlying mechanism by which PUFAs can influence brain function is by their ability to modulate the endocannabinoid system (Bazinet & Layé, 2014). These have been shown to regulate synaptic function by suppressing

neurotransmitter release (Bazinet & Layé, 2014) and they are also involved in synaptic plasticity (Castillo, Younts, Chávez, & Hashimotodani, 2012).

Because DHA concentrations in the brain are so high (Bazinet & Layé, 2014; McNamara & Carlson, 2006; Weiser et al., 2016), a large proportion of research on PUFA actions in the brain has focused on DHA rather than EPA (Dyall, 2015). In animal studies, DHA has been shown to impact a series of mechanisms underlying normal neurological functioning, like for example, neurotransmission (Able et al., 2014), neurogenesis (Calderon & Kim, 2004; Coti Bertrand, O'Kusky, & Innis, 2006; Kawakita, Hashimoto, & Shido, 2006), cell survival (H. Y. Kim, Akbar, Lau, & Edsall, 2000), myelination (Haubner et al., 2007), synaptic plasticity (Bazinet & Layé, 2014) and neuroinflammation (Orr & Bazinet, 2008). Deficiency of DHA, on the other hand, has been associated with compromised neurodevelopment. Igarashi, Santos and Cohen-Cory (2015), for example, observed morphologically simpler tectal neurons with fewer dendrite branches in tadpoles from n-3 PUFA deficient frogs. This process was partially reversed by later feeding them n-3 PUFAs. Depending on the location of these processes within the brain, n-3 PUFA deficiency could affect specific cognitive domains like memory or executive functions. DHA has further been thought to play an essential role in learning and memory, however underlying mechanisms have mainly been studied in animals and are to date not well understood (Fedorova & Salem, 2006). DHA might improve learning and memory by easing the formation of pre- and postsynaptic proteins that are responsible for synaptic transmission and long-term potentiation (Cao et al., 2009).

To date, no unique role of EPA compared to DHA in the brain has been identified, however a series of shared effects with DHA have been described (Dyall, 2015). In rats, DHA and EPA have for example both been associated with increased neurite outgrowth (Robson, Dyall, Sidloff, & Michael-Titus, 2010) and in vitro neurogenesis (Katakura et al., 2013). Similarly, rodent studies have reported associations between both dietary DHA (McGahon, Martin, Horrobin, & Lynch, 1999) and EPA (Martin et al., 2002) intake and benefits to age-related decrease in long-term potentiation (LTP). Furthermore, in terms of anti-inflammatory effects of EPA and DHA seem to be comparable, however, differences concerning their effects in relation to different cytokine ratios exist (Serini et al., 2012). In humans, Borsini, Stangl, Jeffries, Pariante and Thuret (2020) were now able to provide the first evidence that EPA and DHA treatment could prevent cortisol-induced reduction in human hippocampal neurogenesis. These results suggest potential treatment effects of n-3 PUFAs for cognitive complaints in depression, which will be discussed in depth in chapter 1.6.

Adequate intake of n-3 PUFAs, especially DHA, is crucial for normal brain development (J. Baumgartner, 2016; Lauritzen et al., 2016; Sun et al., 2018) and plays an important role during gestation (Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008; Lauritzen & Carlson, 2011), during which the fetus relies on the mother's intake of PUFAs (Hanebutt, Demmelmair, Schiessl, Larqué, & Koletzko, 2008). Especially in late stages of gestation, large amounts of DHA are accumulated in the brain (Kuipers et al., 2012; Lauritzen et al., 2016). Consequently, some maternal supplementation meta-analyses have reported benefits of maternal n-3 PUFA supplementation on child growth and development during pregnancy (Middleton et al., 2019), whereas others reported inconclusive results (Gould, Smithers, & Makrides, 2013). After a child is born, n-3 PUFAs are provided through breast milk or formula, of which many nowadays are supplemented with n-3 PUFAs after research confirmed their vital role in brain development (Qawasmi, Landeros-Weisenberger, Leckman, & Bloch, 2012). The accumulation process of DHA continues at very high rates until the age of about two years (Lauritzen et al., 2016). Evidence, however, remains inconclusive concerning any developmental effects of n-3 PUFA supplementation in infants (Eilander, Hundscheid, Osendarp, Transler, & Zock, 2007; Jiao et al., 2014; Qawasmi et al., 2012; Shulkin et al., 2018; Simmer, 1998). Most robust findings have been reported for effects on visual acuity (European Food Safety Authority, 2009). PUFA metabolism regulation is also crucial for human pubertal brain development due to their involvement in many core elements like myelination or pruning (McNamara & Carlson, 2006; McNamara, Vannest, & Valentine, 2015). Congruently, post-mortem studies have shown that DHA levels in the brain continue to rise during adolescence and reach their maximum at the age of about 20 (Joffre, Nadjar, Lebbadi, Calon, & Laye, 2014). During adolescence, DHA levels have been shown to increase in the frontal cortex (Carver, Benford, Han, & Cantor, 2001). The prefrontal cortex (PFC) is one of the latest brain areas to fully develop, undergoing vast developmental changes during puberty (Kolb et al., 2012). It is also known to be involved in a number of complex cognitive functions like attention, memory, planning and problem solving and is in sum responsible for cognitive control (E. K. Miller & Cohen, 2001). However, it has also been deemed to be especially vulnerable to external factors during development like for example stress, making it especially susceptible to abnormal development (Kolb et al., 2012). The importance of n-3 PUFAs in relation to the PFC and associated cognitive functions has hence been studied in a number of supplementation trials. McNamara and colleagues (2010), for example, found increased functional activation in the dorsolateral prefrontal cortex of healthy children during the performance of a sustained-attention task in the DHA supplemented group compared to the placebo group (McNamara et al., 2010).

As key elements of both structural and functional components of the brain, n-3 PUFAs are essential for normal brain development (J. Baumgartner, 2016; Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008; Lauritzen et al., 2016; Sun et al., 2018). Because brain development continues until the mid 20s (Arain et al., 2013; S. B. Johnson et al., 2009; Sowell et al., 2003; Thompson et al., 2000), children and adolescents might constitute an especially vulnerable group for n-3 PUFA deficiency. n-3 PUFA deficiency might hence have detrimental effects on brain development and might contribute to the emergence of cognitive complaints.

1.2.2 n-3 PUFAs and cognition in youths

Due to their vital role in brain development, n-3 PUFAs have received great attention concerning their potential to benefit cognitive functioning. As has been mentioned earlier, brain development continues until the age of about 25 (Arain et al., 2013; S. B. Johnson et al., 2009; Sowell et al., 2003; Thompson et al., 2000), making youths an especially vulnerable subgroup for n-3 PUFA deficiency. Additionally, cognitive deficits in youths could have long-lasting consequences associated with personal life and educational attainment. At the same time, the developing brain might be more susceptible to change, making supplementation effects of n-3 PUFAs more plausible. The investigation of potential associations between n-3 PUFAs and cognitive functioning in youths has hence gained importance over the last few years. Potential benefits have been studied by the means of associations between n-3 PUFA blood status and cognitive test performance or using supplementation RCTs. In a representative sample of 493 British schoolchildren aged 7-9 years, Montgomery, Burton, Sewell, Spreckelsen and Richardson (2013) were able to identify positive associations between n-3 PUFA status and reading ability as well as working memory. Furthermore, a review by Ramakrishnan, Imhoff-Kunsch and Digirolamo (2009), who studied scientific publications from 1966 to 2008, found that observational studies supported a direct association between low n-3 PUFA levels in children and an increased risk of developing Attention Deficit Hyperactivity Disorder (ADHD), where cognitive complaints are key symptoms. However, evidence from intervention trials only marginally supported this finding (Ramakrishnan et al., 2009).

Conflicting evidence regarding supplementation effects in infants exists. Brew, Toelle, Webb, Almqvist and Marks (2015), for example, found no beneficial effect of about 4.5 years supplementation of n-3 PUFAs starting at the age of about 6 months, on literacy or numeracy in third, fifth, seventh or ninth grade. However, plasma n-3 PUFA levels at the age of 8 years were positively associated with cognitive test scores. Drover, Hoffman, Castañeda, Morale and Birch

(2009), however, reported improved means-end problem solving after n-3 PUFA supplementation when intervention was started early (a few days after birth).

Meta-analytic evidence for supplementation in childhood and adolescence is heterogenous. Jiao and colleagues (2014) who investigated supplementation effects throughout the lifespan, were only able to establish benefits in infants and no other age group. Chang, Su, Mondelli and Pariante (2018), however, reported improved cognitive performances in youths with ADHD after n-3 PUFA supplementation. Conversely, Cooper, Tye, Kuntsi, Vassos, & Asherson (2015) found no beneficial effects of n-3 PUFAs on cognitive performance measures in healthy youths and adults or individuals with ADHD. Short-term memory was, however, improved in individuals with especially low n-3 PUFA status at baseline. A systematic review by Kuratko, Barrett, Nelson and Salem (2013) who investigated DHA supplementation effects in healthy school-aged children, found heterogenous treatment effects, with half of the studies supporting beneficial effects in this population. Van der Wurff, Meyer and de Groot (2020) concluded that efficacy was most probable when more than 450mg of EPA and DHA daily was administered and subjects showed an increase to more than 6% in the omega-3 index. The question remains, whether the specific kind of n-3 PUFA administered and baseline n-3 PUFA levels might play a significant role concerning efficacy of supplementation. In their recent study, Chang and colleagues (2019) for example, reported that especially youths with ADHD with low baseline EPA status achieved higher scores on a continuous performance task after supplementation with high-dose EPA.

Whereas various studies have confirmed the essentiality of n-3 PUFAs in normal brain development, effects of n-3 PUFA supplementation on cognitive functioning in youths have yet to be fully confirmed and understood. Importantly, factors like baseline n-3 PUFA status and effects of select n-3 PUFAs on select cognitive domains might influence supplementation results and are currently subject to extensive investigation. Furthermore, n-3 PUFAs and n-6 PUFAs compete for their position in the membrane, meaning that an excess in either PUFA means that the other can be incorporated only to a lesser extent (Bazinet & Layé, 2014). However, studies eliminating n-6 PUFAs from study formulations or meta-analyses focusing on n-3 PUFA supplementation only are lacking. In sum, beneficial effects of n-3 PUFA supplementation seem most plausible in populations with a poor nutritional status or cognitive complaints compared to healthy populations. However, no meta-analysis so far has investigated differential efficacy between clinical and healthy populations, distinguished between effects of EPA

and DHA and specifically eliminated studies also administering n-6 PUFAs in their study formulations. Based on these research deficits, study 1 was designed. The rationale for study 1 will be discussed in detail in chapter 1.4.

1.2.3 n-3 PUFAs and memory

The previous chapter introduced current knowledge about the effects of n-3 PUFAs on general cognition. Although associations between n-3 PUFAs and many different cognitive domains have been discussed, particularly neuroprotective effects of n-3 PUFAs concerning memory have been suggested. In elderly, memory complaints frequently become evident and can negatively impact quality of life (Alice et al., 2016). However, also at a younger age, memory complaints can emerge, particularly related to psychiatric disorders (Trivedi, 2006).

Current evidence of cognitive decline and Alzheimer's disease was systematically reviewed by Fotuhi, Mohassel and Yaffe (2009) who concluded that observational trials suggested that n-3 PUFA consumption might slow down cognitive decline in elderly individuals but that there was no evidence for the prevention or treatment of dementia or AD in clinical trials. In general, evidence for positive associations between n-3 PUFA status or supplementation and memory in AD has not been proven unequivocally (Itua & Naderali, 2010). However, EPA but not DHA has been negatively associated with grey matter atrophy of the right hippocampal and parahippocampal area and the right amygdala (Samieri et al., 2012). Higher atrophy in the right amygdala was in turn associated with decline in semantic memory performance. In subjects with mild cognitive impairment (MCI), L. K. Lee, Shahar, Chin and Yusoff (2013) reported beneficial effects of 12 months fish oil supplementation on short-term memory, working memory, immediate verbal memory and delayed recall capability. A meta-analysis on healthy adults with or without mild memory complaints (MMC) found that more than one gram per day of DHA and EPA supplementation improved episodic memory regardless of the cognitive status at baseline (Yurko-Mauro, Alexander, & Van Elswyk, 2015). Observational studies supported these findings by providing evidence for positive associations between DHA and EPA intake as well as blood status and memory function (Yurko-Mauro et al., 2015).

Evidence in younger individuals has also proven to be rather inconsistent. Concerning cognitive development, a study investigating perinatal DHA cord status, reported positive associations with memory performance in later childhood (Boucher et al., 2011). As has been mentioned in the previous chapter, n-3 PUFA status has also been positively associated with memory performance in youths (Montgomery et al., 2013), whereas supplementation studies

in young populations have often reported no positive effect of n-3 PUFAs on objective measures of memory performance (J. Baumgartner et al., 2012; Karr, Grindstaff, & Alexander, 2012; Kirby, Woodward, Jackson, Wang, & Crawford, 2010). In their meta-analysis, Jiao and colleagues (2014) reported that there was no evidence for a beneficial effect of n-3 PUFAs on memory performance in youths. The question however remains, whether perinatal supplementation or supplementation at a young age might have long-term neuroprotective effects in later life and whether n-3 PUFAs are associated with memory complaints in relation to psychiatric disorders. While the results reported by Borsini and colleagues (2020) suggest that both EPA and DHA might prevent glucocorticoid-induced reduction in human hippocampal neurogenesis and increase in apoptosis, neuroprotective or direct supplementation effects of n-3 PUFAs in depressed youths have yet to be confirmed. Based on the previously described research deficits, study 2 was designed. The rationale for study 2 will be discussed in detail in chapter 1.7.

1.3 Challenges for cognitive outcome assessment in meta-analyses

In the previous chapters, research on the role of n-3 PUFAs in the brain and associations with cognitive functioning have been discussed. Although cognitive effects as a whole have been suggested, select effects associated with different cognitive domains seem plausible, because effects of n-3 PUFAs might affect select underlying mechanisms of action. Investigating domain-specific associations between n-3 PUFAs and cognitive functioning is, however, associated with certain obstacles that will be delineated in the following chapters. The importance but also the difficulty of the categorization of cognitive domains and associated outcome measures, especially for meta-analyses, are explained and stressed in the following chapters.

1.3.1 Cognitive domains

Cognition as a whole refers to a large set of different, often very specific functions which work together and subserve each other in order to enable an individual to perform certain tasks. The performance levels of the specific functions then add up to produce a certain general level of functioning in an individual. These functions can be grouped together and are then called cognitive domains with the specific functions referred to as subdomains of the larger construct.
Cognitive domains are often hierarchically organized with more basic perceptual functions situated at the bottom, increasing in complexity to domains at the top, like for example cognitive control (Harvey, 2019). The first conceptual question that hence arises for the meta-analytic

evaluation of n-3 PUFA supplementation effects on cognitive test performance is, whether to assess general cognitive functioning as opposed to domain-specific effects. Although supplementation effects of n-3 PUFAs on general cognitive functioning have been suggested, specific effects on select cognitive domains could hint at underlying mechanisms of action and especially affected anatomical regions. Because the developmental course of the brain and the accumulation of n-3 PUFAs during brain development differs between anatomical structures, specific effects related to specific brain areas seem plausible. As has already been mentioned before, an example of a potentially especially affected brain area in youths is the PFC. Hence, investigating domain-specific effects of n-3 PUFA supplementation could prove important in order to capture potentially select effects related to human brain development. Furthermore, clinical trials usually report results for several cognitive functions, however in meta-analyses, several results from a single study cannot be pooled within one analysis. Consequently, investigating effects on general cognitive functioning would lead to the constraint of having to choose which result reported by the specific study to include in the quantitative analysis, giving rise to concern about potential bias related to this selection process. It was therefore decided to investigate domain-specific effects of n-3 PUFA supplementation on cognitive test performance in this dissertation. In order to achieve this, supplementation effects related to specific cognitive functions assessed within clinical trials have to be separated and analyzed using separate meta-analyses. However, separating domain-specific effects is related to some conceptual difficulties. Although the basic concepts of cognitive domains are usually agreed upon, the categorization of the specific functions into cognitive domains and their labelling are not well defined and are often subject to debate. This can lead to diverging concepts in both neuropsychological practice and research, which in turn can largely impact comparability of individual work within the field. For example, divergent classifications in relation to a domain's hierarchical position often occur and sometimes certain domains are also involved in processes related to other domains, which impedes the separation into distinct domains. Attention for example can be classified as an executive function, however attention also plays a key role in many other processes associated with diverse tasks, hence attention is also involved in many other cognitive functions. Remembering a list of words for example, strongly relies on a person's memory capacity but can at the same time not be done without focusing one's attention to the list of words. Whereas executive functions conceptually represent single cognitive domain, they comprise a set of vastly different subdomains including attention but also for example working memory. However, as the name already suggests, working memory is also part of

general memory. This overlap between (theoretically) conceptually different cognitive domains hinders the sharp distinction between them and impedes domain-specific outcome assessment, especially in meta-analyses. Most importantly, it can lead to difficulties in the interpretation and the evaluation of outcome assessments of neuropsychological research, hampering the comparability of study results. Hence, while studies claim the investigation of specific domains, concepts can differ greatly between studies and hence so can results, which leads to decreased comparability. As has been mentioned before, this is especially problematic in meta-analyses where conceptualization and comparability of outcome assessments used by different studies is crucial. For the meta-analysis written as part of this dissertation, the aforementioned difficulties with domain categorization constituted a main obstacle for data analysis. Included studies had to be screened for the exact outcome assessment used and these again had to be categorized within a cognitive domain. Although some outcome measures were clearly associated with the assessment of a certain cognitive domain, others engaged several domains. In order to account for this, specific outcome variables of the same assessment tool were placed in separate cognitive domains. When cognitive domains were assessed using several outcome measures, a decision had to be made which results to include in the quantitative analysis. It was decided to base this decision on the similarity of the assessment tool to the tools from the other trials placed within the domain-specific meta-analysis, in order to increase comparability between results.

In sum, two major obstacles for the investigation of the effects of n-3 PUFA supplementation on cognitive functioning had to be considered for this dissertation. Firstly, a decision had to be made, whether to assess effects on general cognitive functioning or domain-specific effects. Secondly, the categorization process for domain-specific assessment in the meta-analysis was based on some conceptual difficulties related to cognitive functions in neuropsychology, which were carefully considered. The aforementioned difficulties in domain taxonomy are associated with difficulties in outcome assessment using specific measurement tools. Assessing isolated cognitive domains using specific outcome measures is all but trivial and will be discussed in the next chapter.

1.3.2 Measuring cognitive functioning

Although structural and functional neuroimaging has certainly contributed to the understanding of the brain, cognitive functioning and deficits associated with neuropsychiatric diseases cannot be captured fully using imaging only (Fields, Ferman, Boeve, & Smith, 2011). In order to

measure cognitive functioning and cognitive deficits, self-rating questionnaires and objective tests have been used in clinical and scientific settings. Self-rating questionnaires primarily focus on deficits concerning cognitive functioning and tend to assess cognitive complaints that occur in everyday life. As mentioned before, rating scales often include questions concerning abilities relevant in everyday life and hence results obtained through these scales have been shown to be closely linked to for example academic performance (Baars, Nije Bijvank, Tonnaer, & Jolles, 2015). However, these rating scales rely on self-reported information and have been deemed prone to bias, relevant to all forms of self-report scales (Althubaiti, 2016) and validity of assessment can strongly depend on factors like educational status (Spitzer, Weber, & Lutz, 2019) and language proficiency. Also, due to the fact that these cognitive rating scales are strongly deficit orientated, differentiation between average and above average cognitive functioning is often impossible. Even more, difficulties can arise in the assessment of young children, for which the complex language used might be unsuitable and their ability of self-reflection might not be fully developed. Furthermore, age-appropriate self-report measures might not always be available. Based on the aforementioned bias constraints, the young population investigated, and the rather small cognitive deficits expected within this population, this dissertation focused on the investigation of cognitive test performance rather that subjective cognitive complaints.

Objective testing procedures on the other hand, tend to focus less on deficits but capture a broader spectrum of performance. A number of tests have been developed in order to measure global cognitive ability, like for example intelligence tests. These were designed to measure an individuals' general intelligence compared to the average intelligence of the world's population, which is represented using an intelligence quotient (IQ). These objective testing procedures usually comprise a verbal part where skills like general knowledge are assessed and a non-verbal part where skills are assessed which do not directly require verbal information comprehension or production (e.g. problem solving). Especially the verbal part (often referred to as verbal IQ (VIQ)) has been criticized as being confounded by other factors, such as the socioeconomic status of the assessed individual (Dolean & Cãlugãr, 2020). Therefore, it may not reflect fundamental cognitive functioning but rather skills associated with the availability of education and standards of living (von Stumm & Plomin, 2015). Hence, domain-specific measures have gained importance in the assessment of cognitive functioning. For example, in order to measure short-, long-term and working memory, a number of standard tests exist, which can be used in both clinical and scientific settings. Examples are summarized in Table 1.

Table 1
Summary of objective test procedures to measure memory performance

Domain	Name	Description
Short-term memory	Digits forward (e.g. WISC-IV)	A sequence of digits is read out loud and the individual is asked to remember it and repeat it back. The number of digits increases in every second round.
	HVLT-R, RAVLT (VLMT, German version)	A list of nouns is learned over the course of several trials.
Working memory	Digits backwards (e.g. WISC-IV)	A sequence of digits is read out loud and the individual is asked to remember it and repeat it back in reversed order. The number of digits increases in every second round.
	Letter-number sequencing (WISC-IV)	A sequence of letters and numbers is read out loud and the individual is asked to repeat the numbers in ascending order and the letters in alphabetic order.
Long-term memory (recall)	HVLT-R, RAVLT (VLMT, German version)	A list of nouns is learned over the course of several trials. The examinee is asked to recall them after a specific amount of time.

Note. WISC-IV (Wechsler Intelligence Scale for Children, Fourth Edition) (Wechsler, 2003), HVLT-R (Hopkins Verbal Learning Test–Revised) (Benedict, Schretlen, Groninger, & Brandt, 1998), RAVLT (Rey Auditory Verbal Learning Test) (Schmidt, 1996b), VLMT (Helmstaedter & Durwen, 1990)

Compared to subjective ratings of cognitive functioning, objective tests are not prone to the same biases. However, factors like motivation can play an equally large role as in subjective ratings. Also, objective cognitive tests for specific domains are usually biased by global intelligence and hence otherwise evident deficits might be masked by an individual's general cognitive ability. Furthermore, objective tests usually have a large average range and primarily differentiate between average and below or above average scores. Especially in studies with healthy individuals and studies where only small cognitive effects might be expected, this could lead to an underestimation of effects. This is especially true when testing recognition memory, where ceiling effects are very common (Krishnan, Watkins, & Bishop, 2017; Sunderland, Harris, & Baddeley, 1983). Furthermore, testing situations for objective cognitive tests are very artificial. Hence, deficits might well be compensated in the specific test situation, whereas they might become relevant in everyday life. For example, problems concentrating might become evident in a school environment which is busy and loud, whereas these deficits might not be

captured in a quiet examination room without any external distractions. However, objective cognitive tests have often been reported to accurately reflect pathological processes within the brain and strongly predict functional impairment (Fields et al., 2011).

An important issue that has to be kept in mind when using objective test measures of cognitive functioning is construct validity, hence whether the specific test administered actually measures the cognitive outcome it was designed to measure. Categorization of cognitive tests into a specific cognitive domain is not always straight forward because tests often engage several different cognitive domains at the same time. As has already been mentioned in the previous chapter, for example attention processes play an important role in many different test situations. This issue of interconnectivity between cognitive domains can be well illustrated when considering studies in psychiatric patients, that show poor performance in different cognitive tests, which were originally developed in order to measure conceptually different domains (Harvey et al., 2016). Depressed patients for example might show deficits in a short-term memory and attention task, whereas the underlying cause could well be general problems concentrating. Disentangling the proportion of cognitive deficit attributable to memory or attention deficits might hence prove difficult. Further inconsistencies in test reports can arise from definition problems mentioned earlier, where authors claim to have measured for example attention, whereas another researcher might categorize the specific test used into another cognitive domain. This could prove especially detrimental when summarizing study results in meta-analyses, where results wrongly categorized into a specific domain might cancel out results from other studies accurately reporting the cognitive domain tested. The thorough and correct domain categorization of assessment tools was hence made a priority for the meta-analysis written as part of this dissertation.

Another important factor to consider with objective cognitive testing is the establishment of norms for the evaluation of individual test performance. The consideration of an expected "normal" level of functioning related to external individual factors is paramount in order to enable comparability of test results. Evidence for the need of such evaluations was long ago established (Babcoc, 1931). Norms are especially relevant when investigating clinical populations without a healthy control group for comparison. In study 2, this was one of the main reasons for using the VLMT as the outcome measure for verbal memory performance. Although the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 2000) offers many advantages over the VLMT, like for example the evaluation of learning strategies employed, no norms for youths exist for the German version. Another reason constituted the fact that multiple assessments are done over the supplementation period of "the Omega-3 pMDD trial"

and the VLMT offers several parallel versions that can be used to avoid training effects. The VLMT was hence chosen as an objective measure for study 2 in order to assess certain subcategories of verbal memory performance like immediate recall, delayed recall and recognition.
In conclusion, it is safe to say that subjective and objective measures of cognition do not measure the same concepts of cognitive functioning and that they are prone to different kinds of biases. With this in mind, one can argue that an examinee might for example report cognitive complaints in a questionnaire, without any evident deficits in an objective cognitive test measure, for example due to negative self-perception. Especially in the cognitive assessment of clinical populations, like for example patients suffering from MDD, this might pose a serious problem. The assessment of children and adolescents using subjective rating scales might prove even more difficult, because age-appropriate instruments are not always available, and the complex language used in questionnaires might not be fully understood. Also, the ability of self-reflection might be limited in younger children. At the same time, parent-rated questionnaires, especially in clinical populations, might not prove a valid alternative, as has been demonstrated for interviews used for depression severity rating in youths (N. Baumgartner et al., 2020). Furthermore, evaluation of distinct cognitive domains and the consideration of the construct validity as well as demographically corrected norms for the specific test used is paramount. Studies should carefully consider which kind of outcome measure to use in order to assess a specific function and hence be able to draw conclusions considering potentially associated anatomical or functional brain mechanisms involved. Results should hence always be interpreted in relation to the specific measure used. The herein discussed issues of domain-specific outcome assessment were carefully considered when designing both study 1 and 2 and will be further discussed in the following chapter and chapter 1.7 respectively.

1.4 Rationale study 1: n-3 PUFAs and cognitive test performance in youths

The previously discussed research findings and deficits are briefly summarized in the following chapter. Specific research questions for study 1 are described in a second step.

1.4.1 Summary

n-3 PUFAs are part of the lipid bilayer of the brain and have been shown to play an important role during gestation (Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008; Lauritzen & Carlson, 2011) and normal brain development (J. Baumgartner, 2016; Lauritzen et al., 2016)

and are involved in processes related to pubertal brain development (McNamara & Carlson, 2006; McNamara et al., 2015). Due to their crucial role in the brain, associations between n-3 PUFAs and cognitive functioning have been suggested. Because brain development is still ongoing until the mid 20s (Arain et al., 2013; S. B. Johnson et al., 2009; Sowell et al., 2003; Thompson et al., 2000), beneficial n-3 PUFA supplementation effects in youths seem most probable. Also, youths constitute an especially vulnerable subgroup considering cognitive deficits, as they could have detrimental long-lasting effects on educational attainment and everyday functioning. However, both evidence for developmental effects of n-3 PUFA supplementation in infants (Eilander et al., 2007; Jiao et al., 2014; Shulkin et al., 2018; Simmer, 1998) and meta-analytic evidence concerning supplementation in youths seems rather heterogenous (Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015; Jiao et al., 2014). One reason for this might be that supplementation trials often use both n-3 PUFAs as well as n-6 PUFAs in their study formulations (Almaas et al., 2016; Devlin et al., 2017; Stevens et al., 2003), although neurochemical mechanisms differ greatly and it has been shown that incorporation of DHA depends on n-6 PUFA consumption (Simopoulos, 2008). This issue has only been specifically addressed in one previous meta-analysis (Jiao et al., 2014), while others included trials with mixed supplements (Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015). General study heterogeneity concerning n-3 PUFA doses and duration of intervention might have further contributed to the conflicting results, although Jiao and colleagues (2014) reported no association between treatment effect and supplementation dosage. Furthermore, although there are two nutritionally especially important n-3 PUFAs, with large concentration differences within the brain (Bazinet & Layé, 2014; McNamara & Carlson, 2006; Weiser et al., 2016), most meta-analyses to date have reported overall supplementation effects of n-3 PUFAs, disregarding potential efficacy differences (Chang et al., 2018; Jiao et al., 2014). Only Bloch an Qawasmi (2011) suggested that higher doses of EPA were associated with increased efficacy in treating ADHD symptoms and Cooper and colleagues (2015) found that small treatment effects emerged for working memory in studies that supplemented with an adequate amount of EPA. Although beneficial supplementation effects seem most plausible for example in populations with low n-3 PUFA levels (Cooper et al., 2015) or cognitive complaints, most meta-analyses have yet failed to report results in order to compare healthy with clinical populations (Bloch & Qawasmi, 2011; Chang et al., 2018; Jiao et al., 2014). The aim of the first study was to tackle some of the aforementioned research deficits concerning the association between n-3 PUFA and cognitive functioning in youths.

1.4.2 Research questions study 1

In the last few years, research on potential cognitive supplementation benefits of n-3 PUFAs after birth has gained importance. As the number of studies on this matter has exploded, grasping the overall picture has become increasingly difficult. Several meta-analyses have aimed at summarizing results (Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015; Jiao et al., 2014), however coming to heterogenous conclusions. This heterogeneity seems to have arisen from a number of heterogeneities and important shortcomings in study design. These include: 1) Separation of age groups using of an artificial (e.g. legally defined) cut-off of, for example, 18 years of age for adulthood (Cooper et al., 2015) instead of a cut-off based on the developmental course of the brain, 2) Lack of thorough and hence sometimes inaccurate classification of cognitive tests used within cognitive domains (Jiao et al., 2014), 3) Vast differences in study formulations concerning n-3 PUFA dosage, 4) study formulations with both n-3 and n-6 PUFAs (Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015), 5) No comparison between effects in healthy an clinical population within the same study (Bloch & Qawasmi, 2011; Chang et al., 2018; Jiao et al., 2014), 6) No efficacy differentiation between EPA and DHA supplementation (Chang et al., 2018; Jiao et al., 2014), 7) Cognitive assessments based on subjective rating scales (Abdullah, Jowett, Whittaker, & Patterson, 2019; Bloch & Qawasmi, 2011) as opposed to cognitive test performance (Chang et al., 2018; Cooper et al., 2015; Jiao et al., 2014).

The aim of the first research article was to perform a meta-analysis of n-3 PUFA supplementation effects in youths up to the age of 25, using a developmental cut-off for adulthood. It was decided to only investigate cognitive test performance rather than subjective cognitive complaints based on previously discussed concerns about potential bias, hence all studies using questionnaire measures were excluded from analysis. Most importantly, specific effects related to separate cognitive domains were evaluated. A major obstacle to this goal, was a problem mentioned earlier in the introductory section, where studies sometimes claim to have investigated effects concerning a certain cognitive domain, but the specific test used might actually measure cognitive functions more accurately attributed to another cognitive domain. Hence, every single article included in the quantitative analysis was screened for the exact test used and this test was then categorized into a specific cognitive domain. When multiple tests were used in order to measure performance attributable to the same domain, the most similar test to the tests used in other studies was selected in order to maximize comparability. All studies with formulations containing more n-6 PUFAs in the intervention compared to the control group

were excluded. Effects within clinical and healthy subgroups were investigated separately. Further subgroup analyses were performed concerning EPA and DHA supplementation. Especially the categorization into subgroups with EPA-rich and DHA-rich formulations proved rather difficult, because not only n-3 PUFA kind but also concentration varied substantially between study formulations. To our knowledge, no other meta-analysis on the current subject has implemented the same criteria for analysis.

Based on the findings described in the previous chapters, the following research questions for study 1 were developed.

1) Does n-3 PUFA supplementation benefit cognitive test performance in youths?
2) Are there efficacy differences between EPA and DHA supplementation?
3) Are there efficacy differences in clinical versus healthy individuals?
4) Which cognitive domains benefit from n-3 PUFA supplementation?

1.5 Depression

In this chapter, the psychiatric disorder depression is introduced. In a first step, diagnostic concepts and epidemiological data are presented. In a second step, symptoms related to cognitive functioning and current research data on this subject are summarized.

1.5.1 Symptoms and epidemiology

Depression is a common psychiatric disorder that is part of a group of disorders called affective disorders or mood disorders. The main affective disorders are bipolar disorder and depression. Depression is characterized by a set of different symptoms that vary in number and extent throughout affected individuals. To meet the diagnostic criteria for Major Depressive Disorder (MDD) according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), at least five symptoms must have been present for at least two weeks (American Psychiatric Association, 2013). These five symptoms must either include depressed mood or anhedonia (American Psychiatric Association, 2013). For children and adolescents, these key symptoms also include irritable mood (American Psychiatric Association, 2013). DSM-5 defines a catalogue of diagnostic criteria for the diagnosis of depression which are shown in Table 2.

Table 2
Diagnostic criteria for depression defined by the DSM-5

Symptom	Frequency/persistency	Further specifications
Depressed mood	Most of the day, nearly every day	May be subjective (e.g. feels sad, empty, hopeless) or observed by others (e.g. appears tearful); can be irritable mood in children or adolescents.
Markedly diminished interest or pleasure in all, or almost all, activities	Most of the day, nearly every day;	May be subjective or observed by others
Significant weight loss (when not dieting) or weight gain (+/- >5% body weight in a month) or decrease or increase in appetite	Nearly every day	Can be failure to gain weight as expected in children.
Insomnia or hypersomnia	Nearly every day	
Psychomotor agitation or retardation (a slowing down of thought and a reduction of physical movement)	Nearly every day	Observable by others, not merely subjective feelings of restlessness or being slowed down.
Fatigue or loss of energy	Nearly every day	
Feelings of worthlessness or excessive or inappropriate guilt	Nearly every day	Guilt may be delusional; not merely self-reproach or guilt about being sick
Diminished ability to think or concentrate, or indecisiveness Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.	Nearly every day	May be subjective or observed by others.

Adapted from American Psychiatric Association (2013)

Furthermore, it is paramount to be able to differentiate between depression and other psychiatric disorders with similar symptoms, for which purpose further criteria have been specified (see Table 3).

Table 3
Additional diagnostic criteria for differentiation between depression and other psychiatric disorders with similar symptoms

Further criteria
• Symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning • The episode should not be attributable to physiological effects of a substance or another medical condition • The episode should not be better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders • There should also be no history of manic or hypomanic episode; exclusion does not apply if all manic-like or hypomanic-like episodes are substance-induced or are attributable to physiological effects of another medical condition

Note. Adapted from American Psychiatric Association (2013)

These additional requirements serve as an important mean to separate MDD from other psychiatric diseases that may include similar symptoms. For example, bipolar disorder is also characterized by periods of depressed mood, however with manic phases in between. It is also important to rule out depressed symptoms that arise from underlying organic causes or the use of psychotropic substances, in which case MDD is not diagnosed. The same diagnostic criteria are used when diagnosing pediatric major depressive disorder (pMDD) (Thapar, Collishaw, Potter, & Thapar, 2010), however adding irritable mood as one of the key criteria as has been mentioned earlier in the text. Also, children and adolescents can show different signs of depression related to their level of development (Groen & Petermann, 2013). These include frequent somatic symptoms, social isolation, separation anxiety or feelings of boredom (Groen & Petermann, 2013).

Depending on the diagnostic manual used, differences in diagnostic criteria can lead to differential diagnostic outcomes. Both the International Classification of Diseases, Eleventh Revision (ICD-11) (World Health Organization, 2018) and the DSM-5 (American Psychiatric Association, 2013) use categories based on severity, recurrence and the presence of psychotic symptoms. Whereas ICD-11 includes mild depression in the diagnostic catalogue, DSM-5 no longer offers a diagnosis for symptoms with mild severity.

An estimated 10-15% of the world's population is affected by depression at least once during their lifetime (Kessler & Bromet, 2013; Kessler et al., 2015). Prevalence rates in youth have been estimated to lie around 4% with ranges from 0.2% to 17% (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Costello, Egger, & Angold, 2005; Costello, Erkanli, & Angold, 2006; Costello, Mustillo, Keeler, & Angold, 2004). Lifetime prevalence has even been estimated to be as high as 32.5% (Angst et al., 2016) or 41.4% (Moffitt et al., 2010) depending on the study population investigated. When it comes to age distribution, median age of onset typically reported lies in the early to mid 20s (Kessler & Bromet, 2013) with very wide distributions (20-45) (Kessler et al., 2007). However, many patients already report symptoms during adolescence (Kessler et al., 2007; Wittchen et al., 2011) and earlier onset has been associated with poorer health outcomes such as more depressive episodes and more suicide attempts (Zisook et al., 2007). In community samples of children and adolescents, age of onset usually lies around 11 to 14 years of age (Merikangas & Avenevoli, 2003). In severe cases, depression can lead to suicide, which in 2015 was the second leading cause of death amongst 15-29-years-olds (World Health Organization, 2017). In youth, depression has been deemed the leading cause of disability-adjusted life years (DALY) and years lived with disability (YLD) (Erskine et al., 2015). In preadolescence, sex differences seem to play an inferior role compared to adolescence (Merikangas & Avenevoli, 2003), where girls seem to be much more frequently affected than boys (Avenevoli et al., 2015; Breslau et al., 2017; P. Cohen et al., 1993; Kessler & Walters, 1998; Wittchen, Nelson, & Lachner, 1998). Interestingly, sex differences seem to originate in childhood and then grow in magnitude with increasing age (Breslau et al., 2017; Smith, 2009). In terms of course of depression, Curry and colleagues (2011) reported that most adolescents recovered from a depressive episode within 63 months, however cumulative recurrence rate over 4 years was 38.1%. Dunn and Goodyer (2006) reported rather similar recurrence rates for youths in both clinical (44%) and community samples (52%). However, estimations might vary extensively, depending on the method used to define remission and recurrence (Kraus, Kadriu, Lanzenberger, Zarate, & Kasper, 2019).

Despite the severity of this psychiatric disorder, strikingly, it is often neither recognized in adults (Lecrubier, 2007) nor in adolescents (Leaf et al., 1996; E. G. Scott, Luxmore, Alexander, Fenn, & Christopher, 2006), and only about a third of affected adolescents receive appropriate treatment (Costello, He, Sampson, Kessler, & Merikangas, 2014; Ghio, Gotelli, Marcenaro, Amore, & Natta, 2014) with similar numbers observed for adult patients (Lecrubier, 2007).

In conclusion, depression is a very common but also severe psychiatric disorder that in both youths and adults can have serious implications and often remains unrecognized and hence untreated.

1.5.2 Depression and cognition

In chapter 1.5.1 the emphasis was set on emotional symptoms of depression and their potentially disastrous health outcomes. One particular cognitive symptom however, namely problems concentrating, can also have serious implications in daily life and affect personal and social development as well as subjective quality of life (Cambridge, Knight, Mills, & Baune, 2018; Hammar & Årdal, 2009; Knight, Lyrtzis, & Baune, 2020). Especially in children and adolescents neurocognitive complaints can lead to further problems, for example not being able to attend school and hence not reach educational goals, which again can lead to serious social and educational impairments and hence strongly influence quality of life (Fletcher, 2008; Morey-Nase et al., 2019). Functional outcomes in depressed patients often seem to be mediated by these cognitive impairments rather than by emotional symptoms of depression (R. McIntyre, 2014). Morey-Nase and colleagues (2019) reported that for affected adolescents, perceived cognitive impairment seemed to have a bidirectional influence on depression symptomatology and different aspects of quality of life. Additionally, study results have indicated that cognitive impairments might persist even after remission of other symptoms, which may lead to maintenance of these adverse outcomes (Biringer et al., 2007; Bo Jacob Hasselbalch, Knorr, & Kessing, 2011; Semkovska et al., 2019).

A reduced ability to concentrate is a key element in the diagnostic catalogue of depression and diagnosis often depends on the subjective perception and awareness of this impairment. Indeed perceived cognitive impairments are often reported by depressed adults (Iverson & Lam, 2013; R. S. McIntyre et al., 2015) and although studies in younger individuals are rather scarce, they seem to confirm these findings (Morey-Nase et al., 2019). However, especially in depression, self-reports of symptoms might often not validly reflect reality and could be either exaggerated due to negative self-perception (Lahr, Beblo, & Hartje, 2007; Sachs-Ericsson, Joiner, & Blazer, 2008) or underestimated due to for example lack of motivation to cooperate. Furthermore, it remains unknown whether these cognitive complaints are reflected in diminished cognitive test performance. Lahr, Beblo, and Hartje (2007) and Srisurapanont, Suttajit, Eurviriyanukul, and Varnado (2017) for example reported large differences between subjective cognitive complaints and cognitive test performance in adult patients. Evidence from further studies have

tended to underpin these results (R. S. McIntyre et al., 2013; Ott et al., 2016; Svendsen, Kessing, Munkholm, Vinberg, & Miskowiak, 2012). This could mean that patients with large self-reported cognitive complaints might still achieve average scores in neuropsychological test situations. Srisurapanont and colleagues (2017) found that subjective and objective cognitive impairments depended on specific predictors. While depression severity and antidepressant treatment were significant predictors of subjective complaints, age and education were significant predictors of objective cognitive test performance. It has further been debated whether subjective or objective cognitive impairments are more predictive of impaired everyday functioning, with inconsistent results so far (Naismith, Longley, Scott, & Hickie, 2007; Potvin, Charbonneau, Juster, Purdon, & Tourjman, 2016). Together these findings again suggest that self-reported cognitive impairments and cognitive test performance might not reflect the same concept and should be investigated separately (Potvin et al., 2016).

There is, however, vast evidence supporting the notion of poorer cognitive test performance in adult depressed individuals throughout different cognitive domains (Knight & Baune, 2018; R. S. C. Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Marazziti, Consoli, Picchetti, Carlini, & Faravelli, 2010; Rock, Roiser, Riedel, & Blackwell, 2014). Studies have also suggested correlations with indices of illness chronicity like, for example, for memory outcomes (Gorwood, Corruble, Falissard, & Goodwin, 2008). Severity of depression has quite consistently been negatively associated with cognitive test performance (McDermott & Ebmeier, 2009). Yet again, some studies report results where different domains seem less affected or even undisturbed, like for example spatial selective attention (Ladouceur et al., 2012; Olvet, Klein, & Hajcak, 2010). For children and adolescents, results seem even more heterogeneous. Maalouf and colleagues (2011), for example, reported impaired executive functioning in depressed adolescent with tendencies towards negative associations between executive functioning and depression severity. Other cognitive functions like memory and attention however seemed undisturbed. Whereas Goodall and colleagues (2018) and Wagner, Müller, Helmreich, Huss, and Tadić, (2014) reported meta-analytic evidence in favor of deficits in cognitive test performance throughout different domains, Vilgis, Silk, and Vance (2015) found little support for any executive function deficits in children and adolescent according to their narrative review. One explanation for the lack of evidence for impaired cognition in depressed youths might be the shorter depression duration compared to adults, as it has been found to be negatively associated with cognitive functioning (B. J. Hasselbalch, Knorr, Hasselbalch, Gade, & Kessing, 2013). This hypothesis has also been investigated on a neuroanatomical level, providing evidence for

inverse correlations between hippocampal grey matter and duration of depression (Arnone et al., 2013).

Taken together, problems concentrating are a key diagnostic criterion for the diagnosis of depression. These problems are reflected by studies reporting self-reported cognitive complaints in depressed youths as well as adults. Especially in young individuals, studies investigating cognitive test performance have, however, reported mixed results for different cognitive domains. Illness duration might be inversely associated with test performance and hence serve as an explanation for the inconsistent findings concerning cognitive tests performance in youths.

1.5.3 Depression and the brain

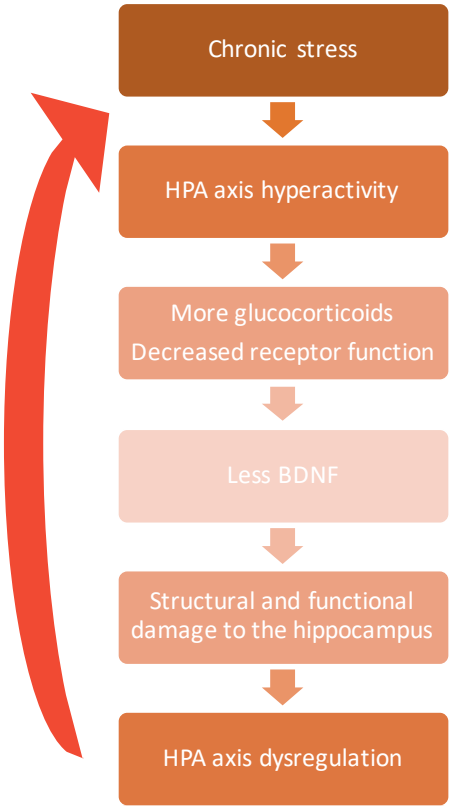
Research on the pathophysiology of depression has investigated underlying neuronal networks that show functional or anatomical alterations in depressed compared to healthy individuals. Clark, Chamberlain and Sahakian (2009) described functional abnormalities in a neural circuit including multiple areas of the PFC, subcortical regions like the thalamus and temporal lobe structures like the hippocampus and the amygdala. In treatment-resistant depression, decreased functional connectivity was found between the hippocampus and limbic regions of the brain (Ge et al., 2019). Clark and colleagues (2009) further concluded that structural abnormalities were mostly found within the fronto-striatal circuitry, with volume reductions in the anterior cingulate cortex. Studies investigating structural abnormalities of the hippocampus have consistently shown depression to be associated with a reduction in the hippocampal volume (Campbell, Marriott, Nahmias, & MacQueen, 2004; Eker & Gonul, 2010; Schmaal et al., 2016; Videbech & Ravnkilde, 2004). Due to its key role in memory function, these anatomical changes have been at least partly made responsible for differences observed in memory test results achieved by depressed individuals compared to healthy controls (Austin, Mitchell, & Goodwin, 2001; Clark et al., 2009; Frodl et al., 2006). Smaller hippocampi in MDD patients have further been associated with earlier age of onset and recurrence of depression (Schmaal et al., 2016). In depressed adolescents, alterations in cortical gray matter have been reported, especially when symptoms were already present at a young age (Schmaal et al., 2017). These findings further stress the importance of early intervention.

Chronic stress has been discussed as a prominent underlying factor, contributing to pathophysiological changes in the brain of depressed patients. Whereas the bodily stress response is a crucial mechanism in humans and animals, persistent stress can have detrimental effects on the human body including the brain (Conrad, 2008). Maladaptive reactions to chronic stress and

the resulting hyperactivity and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in depressed individuals has been associated with impaired forebrain glucocorticoid receptor function which may be one underlying cause for the emergence of depressive symptoms (Boyle et al., 2005; Holsboer, 2013; Kunugi et al., 2006). Chronic stress and maladaptive reactions to it, have been shown to give rise to both structural and functional alterations in the human brain, which then again influence the HPA axis and the body's ability to respond to stress (Ulrich-Lai & Herman, 2009), resulting in a vicious circle. Studies have further shown that chronic stress can lead to the recruitment of additional brain circuits which are then involved in the immediate stress response (Ulrich-Lai & Herman, 2009). It has for example been suggested that chronic stress results in the hippocampus being less involved in the regulation of the HPA axis than without repeated stress exposure (Ulrich-Lai & Herman, 2009). When it comes to cognitive functioning in depression, structural and functional changes in the hippocampus have been deemed to originate from increased glucocorticoid levels (Conrad, 2008). Cortisol has been thought to act as a toxin, progressively contributing to the deterioration of hippocampal grey matter (Conrad, 2008). Further evidence has also suggested altered effects of cortisol on hippocampal function in depressed patients (Abercrombie et al., 2011). Together these alterations have been summarized in a theory called *The Glucocorticoid Vulnerability Hypothesis* which has been reviewed by Conrad (2008).

Neurotrophins play a key role in the maintenance of normal brain functioning as they are involved in neural growth and differentiation and many other plastic and pathological processes reviewed by Chao (2003). Low serum levels of certain neurotrophins like the brain-derived neurotrophic factor (BDNF) have been associated with depression (Molendijk et al., 2011). Chronic stress has been made responsible for the decrease in the expression of neurotrophic factors BDNF which in turn has been linked to atrophy in certain brain regions like the hippocampus or the PFC in depressed patients (Duman & Monteggia, 2006). In a review by Miranda, Morici, Zanoni, and Bekinschtein (2019) BDNF expression, its role in the pathological brain and memory functions are revisited. Figure 2 summarizes the alterations to the HPA axis and interactions with resulting brain anomalies in depressed individuals.

Figure 2
Simplistic model depicting the impact of chronic stress on structural and functional changes to the brain.



In Table 4 alterations related to specific brain regions are summarized.

Table 4
Effects of chronic stress on selected brain areas, the HPA axis and cognitive functioning

Brain area	Effect on the brain	Effect on HPA and cognition
Hippocampus	• Dendritic atrophy • Decreased glucocorticoid receptor expression	• Decreased HPA feedback • Decreased memory
Medial prefrontal cortex (mPFC)	• Dendritic atrophy • Decreased glucocorticoid receptor expression	• Decreased HPA feedback • Decreased memory extinction • Decreased reward
Amygdala	• Increased corticotropin-releasing hormone expression and release • Increased dendritic branching • Increased stress excitability	• Increased HPA autonomic excitability • Increased anxiety • Increased emotional memory • Decreased reward
Thalamus	• Increased stress excitability	• Increased HPA excitability to novel stress • Decreased HPA excitability to familiar stress
Locus coeruleus	• Increased neurotransmitter release • Increased stress excitability	• Increased HPA excitability to novel stress
Hypothalamus	• Increased stress responsiveness • Decreased glucocorticoid receptor expression	• Increased excitability to novel stress

Note. Adapted from Ulrich-Lai & Herman (2009) p. 404

Although glucocorticoids have potent anti-inflammatory effects, the excessive release through the processes of HPA axis dysregulation described above, can lead to increased inflammation and vice versa (Horowitz, Zunszain, Anacker, Musaelyan, & Pariante, 2013; Tapp, Godbout,

& Kokiko-Cochran, 2019) and inflammatory processes have been discussed to play an important role in depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Y. K. Kim, Na, Myint, & Leonard, 2016; Leonard & Maes, 2012; Lotrich, 2015; Rosenblat, Cha, Mansur, & McIntyre, 2014). Evidence of increased inflammation in depressed patients has emerged, following the detection of increased levels of biomarkers of inflammation like interleukins (IL) 6, IL-1- β, C-reactive protein (CRP) and tumour necrosis factor (TNF) α in depressed patients (Iob, Kirschbaum, & Steptoe, 2019; A. H. Miller & Raison, 2016). Inflammation has also been linked to altered neurotransmitter systems involved in for example motivation and anxiety which are important in relation to depression symptomatology (A. H. Miller & Raison, 2016). Correlations between increases in hippocampal volumes and decreases in inflammatory markers following electroconvulsive therapy in depressed patients have been reported (Belge et al., 2020), although recent evidence negates any relationship between inflammatory markers and hippocampal volumes in depressed individuals (Tannous et al., 2020).

Lastly, diminished dopaminergic transmission has been discussed as a further pathophysiological factor in depression and underlying mechanisms have been reviewed by Belujon and Grace (2017) and Dunlop and Nemeroff (2007).

Through complex interactions between the processes discussed in this chapter, functional and structural alterations related to the hippocampus and other brain regions that have been identified in depressed individuals, may be explained. These changes offer pathophysiological explanations for both emotional as well as cognitive complaints, especially mnemonic functions, in depression.

1.6 n-3 PUFAs and psychiatric benefits

A large body of literature has investigated potential beneficial effects of n-3 PUFAs on psychiatric disorders. Psychiatric disorders investigated include bipolar disorder (Clayton et al., 2009), psychotic disorder (Amminger, Schäfer, Schlögelhofer, Klier, & McGorry, 2015), Attention Deficit Hyperactivity Disorder (ADHD) (Chang et al., 2019) and depression (Mocking et al., 2016). In the following chapter, an overview over current research concerning n-3 PUFA and depression is presented.

1.6.1 n-3 PUFAs and depression

As mentioned before, lower n-3 PUFA compared to n-6 PUFA intake over the last two centuries has been associated with the rise of several diseases, including psychiatric diseases like depression (Simopoulos, 2011). Epidemiological studies formed the basis of this area of research, as they reported inverse relationships between oily fish intake and the prevalence (Appleton et al., 2007; Murakami, Miyake, Sasaki, Tanaka, & Arakawa, 2010; Tanskanen, 2001; Timonen, 2004) and incidence (Y. Li, Dai, Ekperi, Dehal, & Zhang, 2011; Sanchez-Villegas et al., 2007) of depression. Meta-analyses have further confirmed negative associations between fish consumption and risk of depression (F. Li, Liu, & Zhang, 2015).

Studies investigating the relationship between n-3 PUFAs and depression have on the one hand focused on differences of the n-3 PUFA status measured in blood and brain between depressed and non-depressed individuals and on the other hand, on the efficacy of supplementation with n-3 PUFAs on symptomatology. Observational studies in adults have reported lower EPA and DHA levels in the blood (Lin, Huang, & Su, 2010; Riemer, Maes, Christophe, & Rief, 2010) as well as in post-mortem orbitofrontal cortex (McNamara et al., 2007, 2013) in depressed individuals compared to healthy controls. Also, Conklin and colleagues (2007) found that higher n-3 PUFA intake was positively associated with a larger grey matter volume in the corticolimbic circuitry. These findings suggest that n-3 PUFA deficiency could have similar consequences for brain development as have been proposed for depression pathophysiology. In youths, evidence seems heterogenic. In 13-25 years old individuals at ultra-high risk for psychosis, Berger and colleagues (2017) found that a high n-6/n-3 ratio at baseline predicted mood disorders over a 7-year follow-up. Pottala and colleagues (2012) reported lower omega-3 indices in depressed individuals aged 13 to 18 years, compared to a healthy control group. Other studies have reported similar results, however only for DHA and not EPA (McNamara et al., 2014). Van der Wurff and colleagues (2019), on the other hand, found no association of neither DHA, EPA or the omega-3 index with depression scores in a random sample of adolescents attending lower general secondary education. These conflicting results might be explained by the influence of other dietary factors. Adjustment for factors like energy intake might mask preliminary results of significant associations between n-3 PUFA status and depression symptoms, like Oddy and colleagues (2011) concluded.

Several meta-analyses investigating supplementation effects of n-3 PUFA on depression in adults have confirmed beneficial effects, with a tendency towards stronger effects for EPA rather than DHA (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019; Martins,

2009; Mocking et al., 2016). Interestingly, symptom severity has been positively associated with treatment effects of n-3 PUFA in depressed individuals (Appleton et al., 2010). In children and adolescents, a meta-analysis summarizing the limited amount of evidence, did not confirm any beneficial effects of n-3 PUFA supplementation in the treatment of depression (Zhang, Liu, Kuang, Meng, & Zhou, 2019). However, conflicting evidence exists, supporting the notion of beneficial supplementation effects in youths (Fristad et al., 2019; McNamara et al., 2014; Nemets, 2006).

Differential effects in n-3 PUFA supplementation trials could be explained by several factors like for example baseline blood levels, differences in trial formulations and individual absorption and utilization rates. As compared to RCTs on for example antidepressants, baseline levels of n-3 PUFA may vary considerably between individuals and are never zero. Hence, the level of n-3 PUFA deficiency might play a role in treatment efficacy, where lower levels might predict stronger benefits (Messamore, Almeida, Jandacek, & McNamara, 2017). Also, study formulations vary significantly regarding fatty acid composition, and meta-analyses have suggested that formulations with larger proportions of EPA rather than DHA might be more effective in the treatment of depression symptoms (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019). Furthermore, little is known about the actual absorption rate and utilization within the brain as well as the influence of the microbiome on PUFA metabolism.

Taken together, studies have shown positive associations of oily fish intake, higher n-3 PUFA status and n-3 PUFA supplementation on depression symptoms. Meta-analytic evidence has suggested tendencies towards beneficial effects of EPA rather than DHA. Results in youths are rather heterogeneous. These discrepancies could have emerged from differences in baseline n-3 PUFA status, differences in study formulations or inter-individual differences in absorption and utilization rates.

1.6.2 Biochemical mechanisms of action

Underlying mechanisms of beneficial effects of n-3 PUFAs on depression symptoms have largely been based on their anti-inflammatory properties (Rapaport et al., 2016), effects on monoamine transmission (Chalon, 2006) and effects on the HPA axis (Larrieu et al., 2014), which are all key factors in MDD psychopathology.

Over the last few years, the monoamine hypothesis has been used dominantly to explain pathophysiology of depression. Consequently, pharmacological treatment with selective serotonin reuptake inhibitors (SSRI), based on the enhancement of serotonergic neurotransmission, have

been deemed the treatment of choice (NICE, 2015). However, a recent meta-analysis by scientists associated with the Nordic Cochrane Centre in Denmark, concluded that there was not enough evidence to conclude that modern day antidepressants are more efficacious than placebo treatment (Munkholm, Paludan-Müller, & Boesen, 2019). These results have received great attention and have been controversially discussed by scientists and clinicians, due to their extensive implications for patients and practitioners. However, these results confirm previous findings of rather large non-response rates to antidepressant therapies (Rush et al., 2008). Several types of antidepressants can furthermore have severe side effects like for example sexual dysfunction (Carvalho, Sharma, Brunoni, Vieta, & Fava, 2016; Outhoff, 2010), nausea (Carvalho et al., 2016), weight changes (Carvalho et al., 2016; Serretti & Porcelli, 2018), sleep disruption (Aszalós, 2006; Carvalho et al., 2016) and even increased suicidality especially in younger individuals (Brent, 2016; Sharma, Guski, Freund, & Gøtzsche, 2016). In Switzerland, no antidepressant medication has been approved for the treatment of pMDD and all prescriptions are hence done off-label, which further emphasizes the need for alternatives. Consequently, n-3 PUFAs have been suggested as an alternative or additional treatment, as they have been shown to affect monoamine transmission, especially in animal models (McNamara et al., 2009; Zimmer et al., 2000). Membrane changes induced by the introduction of larger amounts of n-3 PUFAs, may influence several neurotransmitter systems including dopaminergic and serotonergic pathways, which are of great importance to the pathophysiology of depression. In a rodent model, Chalon (2006) was able to demonstrate that a decrease in brain DHA following deficiency in n-3 PUFA consumption, was followed by a decrease in dopamine in the frontal cortex.

Another factor possibly influencing the development or maintenance of depressive symptoms is linked to inflammatory processes (Leonard & Maes, 2012; Lotrich, 2015; Rosenblat et al., 2014). Current research has broadened the knowledge on brain-inflammation-immune interactions as risk and resilience factors for depressive disorders (for a review refer to Miller & Raison (2016)). Systemic inflammation has been linked to increased depressive symptoms (Beydoun et al., 2019), and n-3 PUFA supplementation has been shown to be able to reduce these inflammatory processes (Natto et al., 2019). Processes involved in this anti-inflammatory effect of n-3 PUFAs are for example the downregulation of n-6 PUFAs and the promotion of proresolvins, neuroprotectins as well as anti-inflammatory mediators (Freeman & Rapaport, 2011; Müller, Myint, & Schwarz, 2009).

Other pathways through which n-3 PUFAs might influence depression pathophysiology include the endocannabinoid system. Studies in rodents have reported depression-like behavior

following a n-3 PUFA deficient diet, potentially explained by the impairment of long-term depression (LTD) in certain brain regions, which is related to the endocannabinoid system (DeMar et al., 2006; Larrieu, Madore, Joffre, & Layé, 2012).

In light of the uncertainty of beneficial effects of traditional antidepressants together with the severe side effects linked to them, alternative or supplementary treatments of depression are needed. The anti-inflammatory properties of n-3 PUFAs may counteract inflammatory processes involved in depression pathophysiology (Grosso, Galvano, et al., 2014). Consequently, n-3 PUFAs have been suggested as a potential treatment option.

1.6.3 n-3 PUFAs and cognitive effects related to depression

In the previous chapters, n-3 PUFAs were introduced and their role in both depression and cognition has been discussed. The question remains as to what extent n-3 PUFAs might be used for the treatment of cognitive complaints in depression. This is of particular interest, as different kinds of antidepressant medication have proven rather heterogeneously effective in the treatment of cognitive problems in depression (Bennabi, Haffen, & Van Waes, 2019; Biringer, Rongve, & Lund, 2009; Bortolato et al., 2016; Prado, Watt, & Crowe, 2018; Rosenblat, Kakar, & McIntyre, 2015; Shilyansky et al., 2016; Skandali et al., 2018; Zuckerman et al., 2018). Furthermore, they have been associated with severe side effects like increased suicidality in youths (Brent, 2016; Sharma et al., 2016). Especially in youths, adverse effects on the brain and cognitive functioning caused by depression could have long-lasting consequences concerning educational attainment and consequently, quality of life. Treatment of cognitive complaints in pMDD could prove especially important concerning the fact that these have been suggested to persist even in the remitted stage (Biringer et al., 2007; Bo Jacob Hasselbalch et al., 2011; Semkovska et al., 2019).

The hippocampus is very important for learning and memory (Bird & Burgess, 2008; Deng, Aimone, & Gage, 2010; Squire, 1992) and both structural and functional changes to the hippocampus have been reported in depressed individuals (discussed in chapter 1.5.3). In the hippocampus, DHA has been made responsible for neuronal development and synaptic function (Cao et al., 2009). Studies in healthy individuals have shown that n-3 PUFA intake (Conklin et al., 2007) but also status (Pottala et al., 2014) are associated with larger hippocampal volumes. Related to cognitive functioning, animal studies have reported improved memory performance following increases in dietary DHA intake and hippocampal DHA levels (Labrousse et al., 2012). DHA deficiency on the other hand has been associated with deficits in dopaminergic

and serotonergic neurotransmission (McNamara et al., 2009; Zimmer et al., 2000), involved in depression pathophysiology (Belujon & Grace, 2017; Dunlop & Nemeroff, 2007), as well as impaired learning and memory (Kuratko et al., 2013). Larrieu and colleagues (2014) reported that n-3 PUFA deficiency in rats leads to both disrupted glucocorticoid receptor mediated signalling and HPA hyperactivity, which in turn resulted in neuronal atrophy in the PFC. Furthermore, EPA but not DHA plasma levels have been associated with lower gray matter atrophy of the right hippocampal and parahippocampal area and of the right amygdala (Samieri et al., 2012) in older subjects. Interestingly, the atrophy in the amygdala was again positively associated with the 4-year decline in semantic memory performances and depressive symptoms. In a recent study, Borsini, Stangl, Jeffries, Pariante and Thuret (2020) were able to provide the first direct evidence for EPA and DHA treatment of cortisol-induced reduction in human hippocampal neurogenesis. These findings summarize the mechanisms suspected to influence functional and structural neurological changes related to n-3 PUFAs, depression and cognition, described in the preceding chapters.

Despite the growing body of evidence suggesting beneficial effects of n-3 PUFAs on cognition and depression symptoms, supplementation studies in depressed individuals seldom report cognitive outcomes (Knochel et al., 2015). Rogers and colleagues (2008) found no benefits of n-3 PUFA supplementation on cognitive symptoms in depressed individuals. Cognitive functioning of recovered (Niki Antypa, Smelt, Strengholt, & Van Der Does, 2012) and adults “at risk” for depression (Duffy et al., 2015) was equally unaffected after n-3 PUFA supplementation. In youths with depression or bipolar disorder however, Vesco, Young, Arnold, and Fristad (2018) reported decreased parent-rated impairments in executive functioning after a 12-weeks supplementation with n-3 PUFAs.

Although a vast body of literature has been able to link n-3 PUFAs to benefits related to depression symptoms as well as cognitive functioning and underlying pathophysiological mechanisms have equally been shown to benefit from adequate n-3 PUFA intake, cognitive effects in depression have been insufficiently studied and current evidence remains inconclusive. Potential protective effects of n-3 PUFAs in relation to cognition in depressed youths could prove especially relevant, considering ongoing brain development in this population, where prevention of, for example, atrophy in the hippocampus would be paramount.

1.7 Rationale study 2: n-3 PUFAs and cognitive test performance in depressed youths

The following chapter gives a brief overview over the previously discussed findings on the association between n-3 PUFAs and cognition in the context of depression. Specific research questions for study 2 are presented in a second step.

1.7.1 Summary

Vast nutritional changes in relation to a decrease of n-3 PUFAs in favor of an increase in n-6 PUFAs within the last century have been associated with the rise of different civilization diseases including depression (Simopoulos, 2011a). Because n-3 PUFA are vital for normal brain development (J. Baumgartner, 2016; Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008; Lauritzen et al., 2016; Sun et al., 2018), potential positive associations between n-3 PUFA and cognitive functioning have been suggested. Positive associations between n-3 PUFA status and cognition have been found in both adults (Cook et al., 2019) and children (Montgomery et al., 2013), however meta-analyses have reported heterogenous results of n-3 PUFA supplementation in youths (Bloch & Qawasmi, 2011; Cooper et al., 2015; Emery et al., 2020; Jiao et al., 2014). Although problems concentrating are part of the diagnostic criteria for depression in both children as well as adults (American Psychiatric Association, 2013), deficits in cognitive test performance have more consistently been reported in adult patient groups (Knight & Baune, 2018; R. S. C. Lee et al., 2012; Marazziti et al., 2010; Rock et al., 2014). Although there is yet no clear understanding of to what degree depressed youths are affected by deficits concerning cognitive test performance, the potential negative impact such deficits might have on their personal and academic development are substantial. Also, it has been established that cognitive deficits might at least partially persist even after remission (Biringer et al., 2007; Bo Jacob Hasselbalch et al., 2011; Semkovska et al., 2019) and hence establishing preventive measures or adequate treatment is paramount. Because antidepressants have proven heterogeneously effective in the treatment of cognitive deficits in depression (Bennabi et al., 2019; Biringer et al., 2009; Bortolato et al., 2016; Prado et al., 2018; Rosenblat et al., 2015; Shilyansky et al., 2016; Skandali et al., 2018; Zuckerman et al., 2018) and potential side effects are unnegotiable, an easily accessible and natural treatment approach could prove important, especially in youths. Current findings have suggested that EPA might be more effective than DHA in the treatment of depression symptoms (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019) and at the same time, beneficial supplementation effects concerning

cognitive functioning have been mostly reported for EPA rather than DHA (Chang et al., 2019; Emery et al., 2020). Despite the importance of an early intervention for cognitive complaints in depressed individuals, only few studies so far have investigated the role of n-3 PUFA in cognitive functioning in depressed populations.

1.7.2 Research questions study 2

Although a vast number of studies has already investigated the effects of n-3 PUFA related to cognition, to date, there has been no study investigating the relationship between n-3 PUFA status and cognition in depressed youths. The aim of study 2 was hence to fill this research gap and investigate associations between n-3 PUFA status and verbal memory performance in a large sample of depressed youths. Study 2 also aimed at investigating potential differences in the association between EPA versus DHA status and cognitive functioning. Based on research in depressed adult patient groups, where depression severity has been negatively associated with cognitive functioning (McDermott & Ebmeier, 2009) and also n-3 PUFA treatment efficacy has been related to severity of depression (Appleton et al., 2010), another aim pursued in paper 2 was to investigate these assumptions in youths.
Based on the literature discussed in previous chapters the following research questions were developed for study 2:

1) Is the DHA and/or EPA status of depressed youths related to their verbal memory performance?
2) Are there association differences between DHA and EPA status concerning verbal memory performance in depressed youths?
3) Is depression severity related to verbal memory performance in depressed youths?
4) Does depression severity impact the association between DHA and/or EPA and verbal memory performance in youths?

Highlighting associations between n-3 PUFA status and cognitive test performance in depressed youths would form the basis for further investigations into supplementation effects in this specific population.

Study 1

Omega-3 and its domain-specific effects on cognitive test performance in youths: A meta-analysis

Sophie Emery, Isabelle Häberling, Gregor Berger, Susanne Walitza, Klaus Schmeck, Therese Albert, Noemi Baumgartner, Michael Strumberger, Mona Albermann, Renate Drechsler

This article was originally published in:

Emery, S., Häberling, I., Berger, G., Walitza, S., Schmeck, K., Albert, T., … Drechsler, R. (2020). Omega-3 and its domain-specific effects on cognitive test performance in youths: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 112, 420–436.* https://doi.org/10.1016/j.neubiorev.2020.02.016

2 Study 1: Omega-3 and its domain-specific effects on cognitive test performance in youths

Abstract

Omega-3 fatty acids are vital for brain development. The aim of this meta-analysis was to broaden current knowledge of the effects of omega-3 supplementation on cognitive test performance in youths. Randomized controlled trials (RCTs) meeting selection criteria were identified through two independent literature searches on PubMed, Cochrane Library, PsycARTICLES and PsycINFO (last search June 2019). Twenty-nine out of 1126 studies assessing 4247 participants met all selection criteria. A meta-analysis using random-effects model was performed for eight different cognitive domains. This first analysis revealed no main effect of omega-3 fatty acid supplementation on domain-specific cognitive test performance in youths. Subgroup analyses identified beneficial effects of eicosapentaenoic acid (EPA)-rich but not docosahexaenoic acid (DHA)-rich formulations in the domains of long-term memory, working memory and problem solving and a tendency towards beneficial effects in clinical rather than non-clinical populations. Future research should investigate differential effects of EPA and DHA and consider their baseline levels, other nutritional components and interactions with gene variations as potential predictors of response.

2.1 Introduction

2.1.1 Background

Impaired cognitive development can severely interfere with everyday life, including school life, work life and social relationships, hence severely impacting quality of life. Due to its critical role in human life, a multitude of studies have attempted to establish factors potentially influencing cognitive development, for example genetics (Mollon et al., 2018); pre- and postnatal factors, such as parental mental health (Mensah & Kiernan, 2010; Wen et al., 2017); or alcohol consumption (Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2017).

Nutrition is one of the most controversially discussed factors thought to influence cognitive development. Dramatic changes in dietary habits over the last two centuries are widely considered to be a major cause of several diseases including diabetes, cardiovascular diseases and cancer (Anderson & Ma, 2009; Simopoulos, 2011a). Consequently, nutrition has also been suggested to influence developmental processes, such as brain maturation during gestation and early childhood (Cusick & Georgieff, 2016). Within nutrition research, the past few years have seen a renewed interest in omega-3 (n-3) polyunsaturated fatty acids (PUFAs), due to the vast changes in dietary habits from a balanced omega-3 to omega-6 ratio to an excess in omega-6 fatty acids in Western societies across the 20th century (Simopoulos, 2011a). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two of the main n-3 PUFAs (Layé et al., 2018). The human body is not able to synthesize these fatty acids by itself and hence relies on the intake of n-3 PUFAs through nutrition (Bazinet & Layé, 2014; Simopoulos, 2011a; Weiser et al., 2016). Indeed, Montgomery, Burton, Sewell, Spreckelsen and Richardson (2013) found an association between low blood n-3 PUFAs and poorer reading abilities and working memory performance in children. Kalmijn et al. (2004) reported an inverse relationship of EPA and DHA consumption with the risk of impaired overall cognitive function and speed at middle age. Moreover, beneficial effects of maternal n-3 PUFA supplementation on child growth and development have been reported (Middleton et al., 2019), suggesting a positive effect on cognitive performance in later life. Consequently, there have been various attempts to enhance cognition through n-3 PUFA supplementation in healthy children and adolescents (M. Johnson, Fransson, Östlund, Areskoug, & Gillberg, 2017; Makrides, Neumann, Simmer, & Gibson, 2000; Osendarp et al., 2007; D. T. Scott et al., 1998; Van Der Merwe et al., 2013) and youths from clinical populations such as ADHD (Bloch & Qawasmi, 2011; Chang et al., 2018). Similarly, treatment effects have been investigated in healthy adults (N Antypa, Van der Does, Smelt, & Rogers, 2009; Bauer et al., 2014) and for the treatment of Alzheimer's disease (Canhada, Castro, Perry, & Luft, 2017; Mazereeuw, Lanctôt, Chau, Swardfager, & Herrmann, 2012). Meta-analyses on the subject report rather heterogeneous results. Jiao et al. (2014) proposed significant positive effects of n-3 PUFA supplementation on cognitive development in infants, yet failed to prove general beneficial effects in other populations and cognitive domains. Findings by Chang et al. (2018) suggest positive effects of n-3 PUFA supplementation on cognitive measures associated with attention in youths with ADHD. Bloch and Qawasmi (2011) also found moderate positive treatment effects for ADHD symptoms, especially with higher doses of EPA, similarly to Grosso, Pajak and colleagues (2014a), Hallahan and

colleagues (2016), Mocking and colleagues (2016) and Liao and colleagues (2019) who reported beneficial effects of EPA on depression symptoms. Meta-analyses focusing on the prevention of cognitive decline were only able to report marginal benefits in specific populations (Mazereeuw et al., 2012), or with specific doses (Abubakari, Naderali, & Naderali, 2014). A recent meta-analysis including both children and adults by Cooper, Tye, Kuntsi, Vassos and Asherson (2015), found no effect of n-3 PUFA supplementation on any cognitive domain, but reported some evidence that only n-3 PUFA deficient populations might benefit from supplementation in terms of enhanced cognitive functioning.

2.1.2 Biological mechanism

PUFAs have diverse effects on various bodily systems. The bioactive roles of EPA and DHA and their bioactive mediators have been extensively reviewed (Dyall, 2015; Layé et al., 2018; Weiser et al., 2016). It is currently widely accepted that n-3 PUFA supplementation results in positive health effects, including benefits to the cardiovascular system (Lovegrove et al., 2004; Massaro et al., 2008; Psota et al., 2006), eye health (Merle et al., 2014), and they give rise to important anti-inflammatory and pro-resolving mediators, reducing inflammation (Bazinet & Layé, 2014; Layé et al., 2018; K. Li et al., 2014). To date, potentially unwanted effects (e.g. decreased blood clotting, decreased blood pressure, diarrhea and acid reflux) have been deemed to be harmless (Bradberry & Hilleman, 2013; Chen, Tofler, McEwen, Ward, & Morel-Kopp, 2013; Clarke, Cullen-Dean, Regelink, Chan, & Rose, 1990; Khodarahm & Azadbakht, 2016; Morris, Sacks, & Rosner, 1993). Conversely, n-6 PUFAs, although also assuming a vital role in bodily functioning, are thought to affect health negatively, mainly due to their proinflammatory and prothrombotic properties (Simopoulos, 2008).

The main PUFAs found in the brain are arachidonic acid (AA), an n-6 PUFA, and docosahexaenoic acid (DHA), an n-3 PUFA (Bazinet & Layé, 2014; Weiser et al., 2016). Within the brain's grey matter, DHA makes up a larger proportion than AA, whereas within white matter, AA is proportionally higher (Bazinet & Layé, 2014; Weiser et al., 2016). EPA, however, exists in a far lower concentration in the brain (Bazinet & Layé, 2014; Weiser et al., 2016). PUFAs are essential for the maturation of the brain during gestation (Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008) and PUFA metabolism regulation is a fundamental process of many core elements of human pubertal brain development, such as myelination and synaptic formation as well as pruning (McNamara & Carlson, 2006; McNamara et al., 2015). Various reviews have summarized the biological role of PUFAs in the brain and their effect on cognitive

functions (Bazinet & Layé, 2014; Bourre, 2004; Janssen & Kiliaan, 2014; Weiser et al., 2016). PUFAs have been found to affect several cellular processes such as membrane fluidity, neuroinflammation, neurotransmitter release, myelination, signal transduction, synaptogenesis and neuronal growth (Dyall, 2015; Weiser et al., 2016). Animal studies have provided vast evidence for the importance of n-3 PUFAs in normal brain developmental processes such as neurogenesis (Coti Bertrand et al., 2006; Kawakita et al., 2006). Igarashi, Santos and Cohen-Cory (2015) found that tadpoles from n-3 PUFA deficient frogs had morphologically simpler tectal neurons with fewer dendrite branches and that this process was partially reversed when they were later fed n-3 PUFAs. Depending on where these cellular processes are taking place, n-3 PUFA deficiency could affect for example memory and executive functioning. Bartl, Walitza and Grünblatt (2014) provided evidence for a protective effect of n-3 PUFAs on pheochromocytoma-12 dopaminergic cell viability in rats. Animal studies also support the association of n-3 PUFA deficiency and impaired learning (Takeuchi, Fukumoto, & Harada, 2002).

The differential effects of EPA and DHA for brain maturational processes are not well understood. Differential effects of DHA and EPA on cell function and health have been extensively reviewed elsewhere (Dyall, 2015; Gorjão et al., 2009; Russell & Bürgin-Maunder, 2012) and have to be taken into account when reviewing the effects of PUFAs on cognition.

Although the findings clearly indicate the crucial role of n-3 PUFAs in human brain biology, the aforementioned meta-analyses have failed to determine consistent beneficial effects of n-3 PUFA supplementation on cognitive functioning throughout the lifespan. Owing to the well-documented importance of n-3 PUFAs in brain maturation and the inconsistent findings relating to their effects on cognition in later life, one might postulate that the effects of EPA and DHA on cognition might change as the brain develops throughout life (Layé et al., 2018). To date, a lack of understanding persists of whether type and ratio of n-3 PUFA supplements, and dosage may contribute to conflicting study results, as has been proposed in relation to primary depression (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019; Mocking et al., 2016; Sublette, Ellis, Geant, & Mann, 2011) and ADHD (Bloch & Qawasmi, 2011). As certain effects have been deemed unique to EPA and DHA, pooling them in meta-analyses seems highly problematic (Dyall, 2015). Furthermore, few researchers have addressed age as a variable, possibly overlooking differential effects for different age groups. Additionally, there has been some disagreement on whether n-3 PUFAs only benefit individuals with deficits in certain cognitive domains, with little to no benefit to individuals with healthy cognition. Lastly, previous meta-analyses have failed to consider the impact of intervention products containing n-6

PUFAs along with n-3 PUFAs, making it impossible to differentiate between their separate effects on cognitive functioning.

2.1.3 Objectives

The aim of this meta-analysis was to broaden current knowledge of the effects of n-3 PUFA supplementation on domain-specific cognitive test performance in children, adolescents and young adults, whose brain maturational processes are still ongoing. We performed separate analyses for specific cognitive domains, in order to avoid random selection of study results for analysis and hence render our results more interpretable. Further, subgroup analyses aimed to examine possible differential effects of EPA-rich and DHA-rich formulations and the effects in non-clinical versus clinical populations. To our knowledge, this is the first meta-analysis to investigate domain-specific effects on cognitive test performance in youths, specifically excluding studies with n-6 PUFA and investigating the differential effects of EPA and DHA and effects in clinical versus non-clinical populations. Evidence supporting a beneficial effect of n-3 PUFAs on cognition in youths could establish the recommendation for a natural and easily accessible nutritional supplement, without any major side effects.

2.2 Methods

2.2.1 Criteria for considering studies for meta-analysis

This systematic review included published randomized controlled trials (RCTs), which investigated the effect of n-3 PUFAs in children and young adults aging from birth up to 25 years of age, as 25 is approximately believed to be the age when most of the brain is fully developed (Arain et al., 2013; S. B. Johnson et al., 2009; Sowell et al., 2003; Thompson et al., 2000). Studies on both healthy subjects and subjects with psychiatric disorders were included. We included all studies with intervention products containing EPA and/or DHA, including fish but no other food products (e.g. walnuts). Only studies assessing cognitive domains through standardized tests were included; all ratings-based studies were excluded. As ratings constitute a measure for externally observable dysfunctions in everyday behavior, rather than a measure of brain functioning, it seemed imperative to exclude questionnaire studies in order to be able to isolate treatment effects on cognitive functioning. Even though this approach might be considered more conservative, the advantage of an objective measure of cognitive functioning seemed

indispensable, as the association between performance measures and rating scales is known to be low (e.g. Krieger & Amador-Campos, 2018). Studies including subjects suffering from severe mental dysfunctions, such as intellectual disability, studies in which infants were supplemented through maternal intake, and studies supplementing more AA in the experimental compared to the control group (due to inconclusiveness on the source of the effect), were excluded from the analysis. Study inclusion parameters disregarded publication year and supplementation time.

2.2.2 Outcome measures

The primary outcome of this systematic review was cognitive functioning. However, cognition summarizes a set of diverse functions controlled by different (sometimes age-related) neural circuits (Samson & Barnes, 2013). Because cognitive functions differ greatly in the brain areas and networks involved as well as their role in everyday functioning and are assessed by fundamentally different cognitive tests, separating the study results into different cognitive domains seemed critical. Also, as there is yet no clear conclusion about potentially select biological effects of n-3 PUFAs on specific brain functions and networks, separate analyses for the different cognitive domains seemed even more important. In cases of studies reporting results for different cognitive tests, we incorporated all results into separate meta-analyses of the specific domains. By doing so, potential selective effects of n-3 PUFAs on different functional networks are considered. The separation process is described in further detail in the results section 2.3.1.

2.2.3 Search methods

An electronic search was conducted by SE and TA individually, which included the following online databases: PubMed, Cochrane Library, PsycARTICLES and PsycINFO. Keywords used in the search included children, adolescents, omega-3, cognition, and related synonyms. For a detailed statement of search (search string) see Appendix A. Other searched resources included recent systematic reviews and related articles, along with pertinent studies referenced therein. The last search was performed on 11 June 2019.

2.2.4 Data collection and analysis

All deviations between the two individual searches were discussed and agreed upon through consensus. Data was managed using RevMan 5.3 (Nordic Cochrane Centre, 2014) and SPSS version 25.0. The change mean and standard deviations from individual cognitive tests were extracted whenever available. Where change scores were not reported, they were calculated using an imputation formula described in the following missing data section. For "development", post-treatment scores were utilized in the meta-analysis, as it was mainly measured and reported post-treatment only, and change and final values should not be mixed in a meta-analysis using standardized mean difference (SMD) as the outcome measure (Deeks, Higgins, & Altman, 2006).

Risk of bias was assessed using the Cochrane risk of bias criteria (Higgins, Altman, & Sterne, 2006). Here, selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases are judged using the levels *low*, *unclear* and *high* risk, based on a set of fixed criteria. For a detailed description, see Appendix B. The bias analysis was performed by SE and IH independently and all disagreements were agreed upon through consensus.

For the measure of treatment effect, SMD was used because although included studies all measured the same cognitive function within one meta-analysis, different tests to assess these functions were used. Effect sizes were categorized as 0.2 representing a small, 0.5 a medium and 0.8 a large effect size (J. Cohen, 1988).

For all cross-over trials, results from the first phase, prior to the cross-over occurring, were incorporated in this meta-analysis. For all other studies with multiple follow-ups, the assessments conducted directly after supplementation ceased were extracted, in order to minimize effect declines.

For all multi-arms trials, the method of splitting placebo groups into approximately equally-sized groups was applied, in order to avoid a unit-of-analysis error (Higgins, Deeks, & Altman, 2006). This is something of a pitfall, because equal means are assumed when using this methods (Rücker, Cates, & Schwarzer, 2017). One of the major drawbacks to using the method is that groups turn out to be correlated. However, the loss of information when combining the intervention groups was considered even more problematic.

All authors who did not report sufficient data (missing change scores, pre- and postscores or number of participants per group), were contacted via e-mail and asked to provide the missing data until one month after request. We received one reply including the required dataset. All other studies had to be excluded from the quantitative analysis. For the few studies reporting

only the number of participants for the placebo and intervention group combined, group sizes were assumed to be distributed similarly to the full data set reported after attrition. For some studies reporting only standard errors, standard deviations were computed using the calculator implemented in RevMan 5.3 (Nordic Cochrane Centre, 2014).

Also, whenever no change scores but only pre- and posttreatment scores were reported, an imputation formula was utilized to calculate the missing within-subject change standard deviation $SD_{change} = SD_{baseline}^2 + SD_{final}^2 - (2 \times Corr \times SD_{baseline} \times SD_{final})$ was computed for the experimental and control group separately (Higgins, Deeks, et al., 2006). The correlation coefficient used in this equation was derived from the "true" correlation coefficient found for the change standard deviations that were reported in some of the included studies. Our analysis of these studies resulted in a mean correlation of 0.649, with the lowest correlation being 0.419 and the highest being 0.940. Therefore, we used a correlation coefficient of 0.6 in the imputation.

Study heterogeneity for each cognitive function was assessed using the Q statistic (a significant statistic indicating heterogeneity) and the percentage of variance due to heterogeneity was evaluated with the I^2 statistic (Deeks et al., 2006).

Reporting bias was evaluated using a funnel plot. A symmetrical appearance of this plot would indicate the absence of reporting bias. A funnel plot was only generated for cognitive domains, with at least ten studies, so that test power would be sufficient and real asymmetry could be distinguished from chance (Sterne, Egger, & Moher, 2006).

We applied a random-effects model (DerSimonian & Laird, 1986) for all cognitive domains for the reason that some heterogeneity might be expected because the studies included slightly different populations and the protocol, along with the supplements themselves, differed between the studies. The true effect that was estimated might hence not be identical between the studies (Deeks et al., 2006).

Subgroup analyses were performed considering possible differential effects of EPA and DHA. Hence, studies were placed in either the "more EPA" or "more DHA" group, depending on the supplementation used. Subgroup analyses were reported for all cognitive domains where at least three studies could be placed in either of the two groups. Additionally, subgroup analyses were computed for clinical versus non-clinical subjects. Studies were placed in the "non-clinical" group if the participants included were not chosen due to specific health problems that were of interest to the investigators. Conversely, studies were placed in the "clinical" group, if they investigated the effect of n-3 PUFA in a population with a specific health problem. Again,

these analyses were performed for all cognitive domains with at least three studies in either group. Furthermore, results from studies supplementing less than 400 mg of daily DHA and EPA combined were excluded from the analysis to assess whether a minimum dose is needed in order for the supplementation to be effective. We chose a 400 mg cut-off following results reported by Bloch and Qawasmi (2011) who found EPA doses from around 400 mg and up to be the most effective. Dosage trends were also examined through comparing dose size in relation to the measured effect, in order to determine whether higher doses are more effective. Lastly, we investigated possible moderating variables by correlating them with the effect sizes found in each study.

A sensitivity analysis for the imputation of within-subject change standard deviations was performed using a correlation coefficient of 0.5, in order to assess the robustness of the results. The sensitivity analysis yielded a maximum effect size difference of 0.03, which was considered satisfactory, as most of the cognitive domains either exhibited no variance, or no more than 0.01–0.02. Another sensitivity analysis was performed for all studies indicating a substantial amount of heterogeneity ($I^2 > 50$ %) using random-effects model, by individually removing every study and checking for substantial effect size and heterogeneity changes.

It was decided that the best procedure to investigate moderating variables was to look for any associations through correlations and then potentially perform further analyses, should any significant correlations be identified. We chose to investigate whether the duration of supplementation or the year of publication might be associated with the effect size of the studies.

2.3 Results

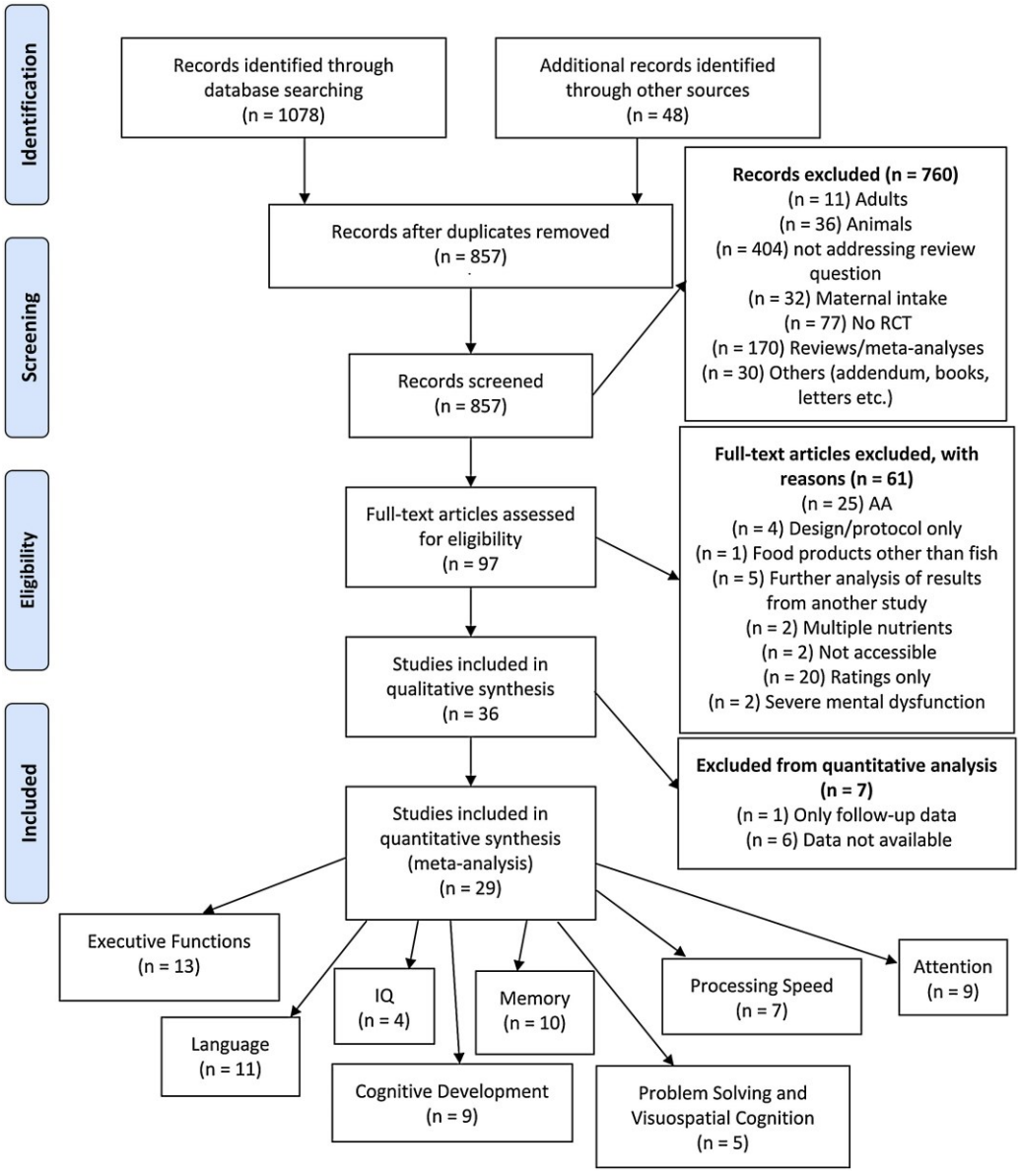
2.3.1 Description of the studies

The literature search yielded a total of 1078 records, along with 48 additional records that were identified through other sources (cross-referencing other meta-analyses). After exclusion of 821 articles (see Figure 3), 36 were included in the qualitative analysis. Out of these, 7 had to be excluded from the quantitative analysis due to missing data (Birch et al., 2007; Bos et al., 2015; Brew et al., 2015; Hirayama, Hamazaki, & Terasawa, 2004; Leutgeb, Köchel, Lang, Koch, & Schienle, 2015; Milte et al., 2012; Ryan & Nelson, 2008). In the end, 29 studies were included in the quantitative analysis (J. Baumgartner et al., 2012; Birch, Garfield, Hoffman, Uauy, & Birch, 2000; Carlson & Werkman, 1996; Cornu et al., 2018; Crippa et al., 2019; Demmelmair et al., 2019; Handeland et al., 2017; Harbild, Harsløf, Christensen, Kannass, &

Lauritzen, 2013; M. Johnson et al., 2017; Karr et al., 2012; Kean et al., 2017; Kennedy et al., 2009; Kirby et al., 2010; Makrides et al., 2000; McNamara et al., 2010; Meldrum et al., 2012; Osendarp et al., 2007; Øyen et al., 2018; Parletta, Cooper, Gent, Petkov, & O'Dea, 2013; Portillo-Reyes, Perez-Garcia, Loya-Mendez, & Puente, 2014; Richardson, Burton, Sewell, Spreckelsen, & Montgomery, 2012; Richardson & Montgomery, 2005; D. T. Scott et al., 1998; Sinn, Bryan, & Wilson, 2008; Vaisman et al., 2008; Van Der Merwe et al., 2013; Voigt et al., 2001; Werkman & Carlson, 1996; Widenhorn-Müller, Schwanda, Scholz, Spitzer, & Bode, 2014). For a more detailed description of the inclusion/exclusion process see Figure 3.

Figure 3

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Moher, Liberati, Tetzlaff, & Altman, 2009)



A summary of the studies' characteristics is provided in Table 5. Overall, the 29 studies included 4247 participants, ranging in age from birth to 20.43 years. These participants were treated with either the intervention product or the control product for four to 48 weeks. 13 studies used more EPA than DHA in their interventions, and 17 studies used the inverse in their interventions. One study created two intervention groups, where one received more DHA and the other more EPA. Out of the 29 included studies, 13 assessed executive functions, 11 language skills, four intelligence (IQ), nine cognitive development, 10 memory function, five problem solving and visuospatial cognition, seven processing speed and nine attention. From these, the following eight cognitive domains for the meta-analyses were established: Attention; general cognitive ability (IQ); memory (short-term, long-term, recognition); executive functions (working memory, shifting/flexibility, inhibition); cognitive development, language (general, reading, spelling); processing speed and problem solving, and visuospatial cognition. A detailed list of cognitive functions and related tests are provided in Appendix C. For further details on all included studies, refer to Table 6.

Table 5
Summary of baseline characteristics of included studies

Characteristics	Included studies
Publication year range	1996 - 2019
No. of participants	4247
Age range of means	Birth – 20.43 years
Number of studies with non-clinical / clinical participants[1]	16 / 14
EPA dose range per day[2, 3]	0-720 mg / day
DHA dose range per day[2, 3]	0-1200 mg /day
n-3 PUFA dose range per day (combined)[2, 3]	94.29 mg – 1200 mg
Number of studies with more EPA / more DHA[1]	13 / 17
Treatment duration range	4 – 48 weeks

Note. All numbers refer to baseline characteristics.

[1] One study included twice because both apply

[2] Formula supplements were excluded from this statistic

[3] For studies that did not administer the supplement daily, the daily dose was calculated by dividing the weekly dose by seven

Table 6

Baseline characteristics of all included studies and those excluded due to missing data.

Author (year) country	Type of participants	Age at baseline	% females per group	No. of participants	Omega-3 daily dose	EPA : DHA ratio	Control	Treatment duration	Tests used	Subtests/measurements
Kean (2017) AUS	Symptoms of inattention and hyperactivity	M = 8.82 SD = 2.27	E: 23% C: 6%	E: 54 C: 58	≤ 45 kg: 140.4 mg EPA, 109.2 mg DHA > 45kg: 187.2 mg EPA, 145.6 mg DHA	1.29 : 1	olive oil, lecithin, coconut oil and beta-carotene	14 wk	1: COMPASS Cognitive Test Battery 2: TOVA	1: word and picture presentation, immediate word recall, simple and choice reaction time, numeric working memory, delayed word recall, delayed word and picture recognition
Portillo-Reyes (2014) MEX	Malnourished children	M_E = 9.3 SD_E = 1.17 M_C = 9.08 SD_C = 0.99	E: 34% C: 24%	E: 30 C: 25	180 mg DHA and 270 mg EPA	1.5 : 1	soybean oil capsules	3 mos.	1: WISC-IV 2: ENI 3: Letter cancellation 4: Rey complex figures 5: Word list 6: Semantic fluency 7: Matrix reasoning 8: Letter–number sequencing 9: Stroop color and word test 10: TMT-A and TMT-B	1: Symbol search and Block design 2: Embedded figures test, visual closure, comprehension instruction
Baumgartner (2012) ZAF	children with poor iron and n-3 FA status	M_E = 8.9 SD_E = 1.3 M_C = 9.1 SD_C = 1.4	E: 43% C: 47%	E: 81 C: 80	420 mg DHA, 80 mg EPA on 4d/wk	0.19 : 1	medium-chain triglycerides	8.5 mos.	1: KABC-II 2: HVLT	1: Atlantis, Atlantis Delayed, Hand movement test, Triangles test 2: recall, delayed recognition

Table 6
continued

Kennedy (2009) UK	Healthy	M_{E1} = 11.11 SD_{E1} = 0.79 M_{E2} = 10.70 SD_{E2} = 0.79 M_C = 10.87 SD_C = 1.01	E_1: 32% E_2: 50% C: 60%	E_1: 28 E_2: 30 C: 30	400mg DHA or 1000mg DHA capsules	1 : 50	Capsules with vegetable oil	8 wk	1: Internet Battery 2: Cognitive Drug Research Battery (CDR)	1: Word and Picture Presentation, Arrow Reaction Time and Flanker Test, Paired Associate Learning, Sentence Verification, Delayed Word and Picture Recognition 2: Picture Presentation, Word Presentation/Immediate word recall, simple and choice reaction time, spatial and numeric working memory, delayed word recall, delayed word and picture recognition
Osendarp (2007) AUS and IND	AUS: healthy IND: marginally-nourished	AUS: M_E = 8.8 SD_E = 1.0 M_C = 8.5 SD_C = 1.0 IND: M_E = 8.1 SD_E = 1.1 M_C = 8.1 SD_C = 1.1	AUS: E: 45% C: 39% IND: E: 52% C: 50%	AUS: E: 67 C: 71 IND: E: 94 C: 88	88 mg DHA and 22 mg EPA (AUS daily, IND 6d/wk)	0.25 : 1	fruit-flavored drink (soy 0.6%)	12 mos.	Factor scores for several cognitive tests combined	
Karr (2012) USA	Healthy	M_E = 19.9 SD_E = 1.83 M_C = 20.43 SD_C = 1.63	E: 75% C: 67%	E: 20 C: 21	480 mg DHA, 720 mg EPA	1.5 : 1	Coconut oil	4 wk	1: RAVLT 2: Stroop Color-Word Test 3: TMT-A and B	1: Memory score after stage 5, delayed-recall score
Meldrum (2012) AUS	Healthy	Birth	E: 48% C: 48%	E: 138 C: 149	at least 250 mg DHA and 60 mg EPA	0.24 : 1	Olive oil	6 mos.	Bayley Scales of Infant Development III	Cognitive and language composite score

Table 6 continued

Birch (2000) USA	Healthy	M = 2.1 d SD = 1.0	E: 59% C: 55%	E: 26 C: 26	formula milk supplemented with 0.35% DHA	0 : 1	control formula without DHA	17 wk	Bayley Scales of Infant Development 2nd edition	MDI, cognitive composite score, language composite score
Scott (1998) USA	Healthy	M_E = 2.6 d SD_E = 1.9 M_C = 3.2 d SD_C = 2.5	E: 40% C: 46%	E: 43 C: 45	formula with 0.2% DHA from fish oil	0 : 1	Unsup-ple-mented formula	12 mos.	Bayley Scales of Infant Development 2nd edition	MDI
Makrides (2000) AUS	Healthy	1 wk	E: 48% C: 48%	E: 23 C: 21	Formula with 0.35% DHA	0 : 1	Unsup-ple-mented formula	12 mos.	Bayley Scales of Infant Development 2nd edition	MDI
Øyen (2018) NOR	Healthy	M_E = 5.2 SD_E = 0.6 M_C = 5.2 SD_C = 0.6	E: 53% C: 59%	E: 105 C: 113	3/wk fatty fish, approx. 1081 mg EPA and DHA per serv-ing	More DHA than EPA	meat (chicken/ lamb/bee f)	16 wk	WPPSI-III	Total raw score, verbal raw score, performance raw score, processing speed raw score
Cornu (2018) FRA	ADHD	M_E = 10.2 SD_E = 2.8 M_C = 9.7 SD_C = 2.5	E: 24% C: 19%	E: 80 C: 82	6–8 y: EPA 336 mg, DHA 84 mg; 9–11 y: EPA 504 mg, DHA 126 mg 12–15 y: EPA 672 mg and DHA 168 mg	4 : 1	Olive oil capsules	3 mos.	1: Alouette test 2: KiTAP	2: Flexibility, Go-/No-Go, Distractability
Richardson (2012) UK	Underper-forming in reading	M_E = 103.7 mos. SD_E = 10.0 M_C = 104.8 mos. SD_C = 10.1	E: 47% C: 47%	E: 180 C: 182	600 mg DHA	0 : 1	corn/soy-bean oil	16 wk	1: British Ability Scales (BAS II)	1: Word reading achieve-ment sub-test, Recall of Digits Forward, Recall of Digits Backward
Kirby (2010) UK	Healthy	M_E = 9.17 SD_E = 0.57 M_C = 9.08 SD_C = 0.56	E: 53% C: 51%	E: 171 C: 177	DHA 400 mg, EPA 56 mg	0.14 : 1	Olive oil	16 wk	1: WIAT-II 2: WMTB-C 3: TEA-Ch	1: word reading, pseudo word reading, spelling 2: digit recall, block recall, backward digit recall 3: Creature Counting

Table 6 continued

Werkman (1996) USA	Preterm infants	M = 25d	E: 61% C: 65%	E: 33 C: 34	0.2% DHA formula	0 : 1	Unsupplemented formula	9 mos. main source of nutrients. Mixed diet until 12 mos.	Fagan Test of Infant Intelligence	Novelty preference
Carlson (1996) USA	Preterm infants	Approx. 3d	E: 47% C: 42%	E: 15 C: 12	0.2% DHA formula	1 : 3.33	Unsupplemented formula	2 mos.	Fagan Test of Infant Intelligence	Novelty preference
Handeland (2017) NOR	healthy	M_{E1} = 14.6 SD_{E1} = 0.3 M_{E2} = 14.6 SD_{E2} = 0.3 M_C = 14.6 SD_C = 0.3	E_1: 56% E_2: 53% C: 51%	E_1: 137 E_2: 141 C: 148	Fish meal 152.3 mg/100 g EPA, 262.3 mg/100 g DHA (one meal is 230g) or 7 capsules (each 158 mg EPA, 105 mg DHA, 13 mg DPA) (3/week)	Meal: 0.58 : 1 Capsules 1.5: 1	Meat meals	12 wk	d2 test of attention	Total performance (TN-E)
Widenhorn-Müller (2014) DEU	ADHD	M_E = 8.90 SD_E = 1.48 M_C = 8.92 SD_C = 1.24	E: 24% C: 21%	E: 46 C: 49	600 mg EPA, 120 mg DHA	5 : 1	Olive oil	16 wk	1: HAWIK-IV 2: TAP/KiTAP	1: Processing speed index score, Digit Span Forward, Digit Span Backwards
Van der Merwe (2013) GMB	healthy	M_E = 92.3d SD_E = 4.25 M_C = 93.2d SD_C = 4.22	E: 44% C: 41%	E: 90 C: 90	200 mg DHA and 300 mg EPA	1.5 : 1	Olive oil	6 mos.	1: Willatts' Infant Planning Test 2: Toddler attention assessment	1: Average total intention score 2: Inattention rate
McNamara (2010) USA	Healthy boys	M_{E1} = 9.2 SD_{E1} = 1.0 M_{E2} = 9.5 SD_{E2} = 0.7 M_C = 8.8 SD_C = 0.8	E: 0% C: 0%	E_1: 12 E_2: 14 C: 12	400 mg or 1200 mg DHA mg	0 : 1	Corn oil	8 wk	CPT-IP	Commission errors

Table 6
continued

Vaisman (2008) ISR	impaired visual sustained attention performance	M_{E1} = 9.17 SD_{E1} = 1.27 M_{E2} = 9.40 SD_{E2} = 1.06 M_C = 9.31 SD_C = 1.28	E_1: 17% E_2: 29% C: 29%	E_1: 18 E_2: 21 C: 21	PL-n-3: 156 mg EPA, 95 mg DHA FO: 153 mg EPA, 96 mg DHA	PL-n-3 group: 1.64 : 1 FO group: 1.59 : 1	rapeseed oil	3 mos.	TOVA	Errors of omission, errors of commission
Voigt (2001) USA	ADHD	M_E = 9.1 SD_E = 2.1 M_C = 95 SD_C = 1.7	E: 22% C: 22%	E: 27 T: 27	DHA 345 mg	0 : 1	Placebo not further specified	4 mos.	1: TOVA 2: Children's Color Trails Test	1: Errors of omission, errors of commission 2: A and B
Harbild (2013)	Healthy	9 mos.	E: 55% C: 48%	E: 38 C: 44	465mg DHA and 697 mg EPA	1.5 : 1	No supplementation	3 mos.	Single object free play task	
Sinn (2008) AUS	ADHD	M_E = 9.38 SD_E = 1.89 M_C = 9.47 SD_C = 1.83	E: 27% C: 21%	E: 37 C: 28	EPA 93 mg, DHA 29 mg, GLA 10 mg	3.21 : 1	palm oil	15 wk	1: WISC-III 2: RAVLT 3: TEA-ch 4: NEPSY 5: Stroop color-word test 6: Inspection time	1: Vocabulary, Block Design, Digit-Symbol Coding, Digit Span Backward and IQ estimate 2: total recall, delayed recall and recognition 3: Creature Counting 4: Knock and Tap
Parletta (2013) AU	Healthy	3-13	E: 47% C: 46%	E: 147 C: 163	EPA 558 mg, DHA 174 mg, GLA 60 mg per school day	3.21 : 1	Palm oil	20 school weeks (crossover to fish after that)	WRAT4: reading and spelling, Draw-a-person (development)	
Johnson (2017) SWE	Healthy	9-10	E: 49% C: 51%	E: 78 C: 76	558 mg EPA, 174 mg DHA, 60 mg GLA	3.21 : 1	Palm oil	3 mos. (crossover to active after)	Logos Test	Reading, listening comprehension, vocabulary, verbal short-term memory

Table 6 continued

Richardson (2005) UK	Suspected: developmental coordination disorder type difficulties	*M*: 105.8 mos. *SD*: 16.3	33%	E: 55 C: 57	558 mg EPA, 174 mg DHA, GLA 60 mg	3.21 : 1	Olive oil	3 mos. (crossover to active after)	Wechsler Objective Reading Dimensions (WORD)	Reading age, Spelling age
Crippa (2019) ITA	ADHD	M_E = 11.06 SD_E = 1.85 M_C = 10.91 SD_C = 1.42	E: 8% C: 8%	E: 25 C: 25	500 mg DHA	0 : 1	Germ oil	6 mos	1: ANT 2: Battery for the Assessment of Developmental Reading and Spelling Disorder	1: baseline speed, focused attention 4 letters, shifting attentional set – visual, sustained attention 2: reading speed, reading accuracy
Demmelmair (2018) GER	Healthy	Mdn_E = 4.9 IQR_E = 0.8 Mdn_C = 5.0 IQR_C = 0.8	E: 47.9% C: 52.7%	E: 96 C: 93	303.1mg EPA, 538.9mg DHA per meal, 3/week	0.56 : 1	Meat	16 wk	WPPSI-III (HAWIWA-III)	FIQ, VIQ, PIQ, PSQ
					Excluded studies due to missing data					
Bos (2015)	ADHD	M_E = 10.3 SD_E = 2.0 M_C = 10.9 SD_C = 2.0	E: 0% C: 0%	E: 40 C: 39	650 mg DHA and 650 mg EPA	1 : 1	margarine	16 wk	Go/No-Go Task	
Leutgeb (2015) AUT	Healthy	*M* = 62.2 mos. *SD* = 8.5	E: 49% C: 66%	E: 35 C: 35	600 mg EPA, 200 mg DHA	3 : 1	Waiting list	8 wk	WET (Wiener Entwicklungstest): 1: Zahlen merken 2: Muster legen 3: Bunte Formen	
Birch (2007) USA	healthy	*M* = 2.1d *SD* = 1d	E: 56% C: 53%	E: 26 C: 26	0.35% DHA formula	0 : 1	Non-supplemented formula	17 wk	WPPSI-R	VIQ, PIQ, FIQ
Brew (2015) AUS	Healthy (family history of asthma)	from the time breastfeeding ceased or at 6 mos.	47%	E: 118 C: 121	135 mg of DHA and 32 mg of EPA per capsule	0.24 : 1	Sunola oil	Approx. 4.5 y	NAPLAN	

Table 6 continued

Milte (2012) AUS	ADHD	M_{E1} = 8.77 SD_{E1} = 1.76 M_{E2} = 8.89 SD_{E2} = 1.6 M_C = 9.13 SD_C = 2.03	E_1: 20% E_2: 25% C: 17%	E_1: 30 E_2: 28 C: 29	1109 mg EPA and 108 mg DHA or 264 EPA mg and 1032 mg DHA	10.27 : 1 or 0.26 : 1	safflower oil provid-ing LA 1467 mg/d	4 mos.	1: TEA-ch 2: WIAT-III 3: Go/no-go task 4: WISC-III	1: Creature Counting, Sky Search, Score!, Sky Search DT 2: Reading and Spelling subscale 4: Vocabulary subscale
Hirayama (2004) JPN	ADHD	6-12 (*M*: 9.0)	E: 20% C: 20%	E: 20 C: 20	514.29 mg DHA, 100 mg EPA	0.19 : 1	placebo foods contain-ing olive oil	2 mos.	1: Memorizing digits 2: CPT	1: visual and auditory
Ryan (2008) USA	Healthy	M_E = 52.0 mos. SD_E = 2.3 M_C = 51.4 mos. SD_C = 2.4	E: 49% C: 50%	E: 85 C: 90	400 mg DHA	0 : 1	high-oleic sun-flower oil	4 mos.	1: Leiter-R 2: PPVT 3: Stroop Day-Night Test 4: kCPT	1: Attention Sustained

Note. Age means and standard deviations are given in years if not otherwise indicated. Where only age ranges are given, means and standard deviations were not reported in article. "E" refers to the experimental group and "C" refers to the control group. All characteristics for other irrelevant interventions and/or control groups (breast milk, other nutrients etc.) were omitted. GLA refers to gamma linolenic acid, FO = fish oil, MDI = mental development index, VIQ = verbal IQ, PIQ = performance IQ, FIQ = full scale IQ.

2.3.2 Risk of bias

According to the Cochrane Risk of Bias Criteria (Appendix A), four studies were rated *low* across all bias risks (Cornu et al., 2018; McNamara et al., 2010; Richardson et al., 2012; Van Der Merwe et al., 2013). "Selective reporting" was the criterion most frequently rated *unclear*, whereas "incomplete outcome data" and "blinding of participants and personnel" were the criteria most frequently rated *high*. Appendix D. Fig. 1 provides a more detailed summary on the proportion of suspected biases for the included studies.

2.3.3 Main analysis results

The meta-analyses revealed no main effect of n-3 PUFA supplementation for any of the cognitive domains. The number of studies included in one meta-analysis ranged from three (spelling) to 14 (inhibition) and SMDs ranged from −0.07 (95 % CI: −0.25, 0.11) for language to 0.13 (95 % CI: −0.05, 0.32) for long-term memory (recall). Most analyses resulted in satisfactory heterogeneity, except for the analyses on problem solving and visuospatial cognition, and reading. All results for the main analyses are summarized in Table 7.

Table 7
Main treatment effect for all cognitive domains.

Domain	*n* studies[a]	Effects of intervention			Heterogeneity	
		SMD	95% CI	*p*	I^2	*p*
Long-term memory (recall)	6	0.13	-0.05, 0.32	.16	9%	0.65
Working memory	7	0.12	-0.05, 0.29	.16	33%	0.18
Shifting/Flexibility	7	0.12	-0.08, 0.32	.25	38%	0.14
Problem solving and visuospatial cognition	5	0.12	-0.10, 0.34	.27	51%	0.08
Development	9	0.11	-0.10, 0.23	.08	2%	0.42
Long-term memory (recognition)	5	0.11	-0.12, 0.35	.35	22%	0.28
Processing speed	7	0.09	-0.06, 0.24	.25	0%	0.97
Short-term memory	12	0.08	-0.02, 0.17	.14	0%	0.92
Reading	7	0.07	-0.09, 0.23	.40	51%	0.06
Spelling	3	0.05	-0.12, 0.21	.58	24%	0.27
Attention	13	0.00	-0.12, 0.12	.98	0%	0.54
IQ	5	0.00	-0.14, 0.14	.97	0%	0.45
Inhibition	14	0.00	-0.18, 0.19	.98	37%	0.08
Language	7	-0.07	-0.25, 0.11	.44	28%	0.21

[a]Results for different treatment groups were counted as separate studies

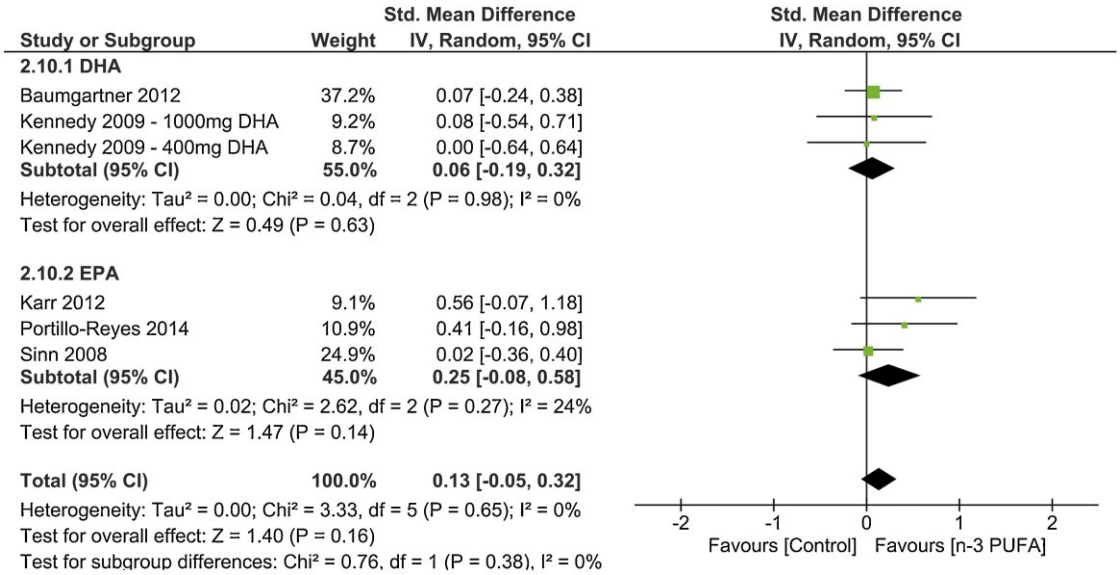
2.3.4 EPA-rich versus DHA-rich formulations

To address the issue of differential effects of EPA and DHA, a subgroup analysis was performed by categorizing the studies according to whether EPA or DHA content was higher in the supplementation product. The subgroup analysis resulted in small effects for the EPA group in the cognitive domains of long-term memory (recall) (SMD of 0.25 (95 % CI: −0.08, 0.58)) (Figure 4), working memory (SMD of 0.36 (95 % CI: 0.09, 0.63)) (Figure 5) and problem solving (SMD of 0.21 (95 % CI: −0.21, 0.64)) (Figure 6) with satisfactory heterogeneities of I^2 = 24 %, p = 0.27 and I^2 = 0 %, p = 0.39 for long-term memory (recall) and

working memory respectively. The meta-analysis on problem solving however, was significantly heterogeneous (I^2 = 71 %, p = 0.03).

Figure 4

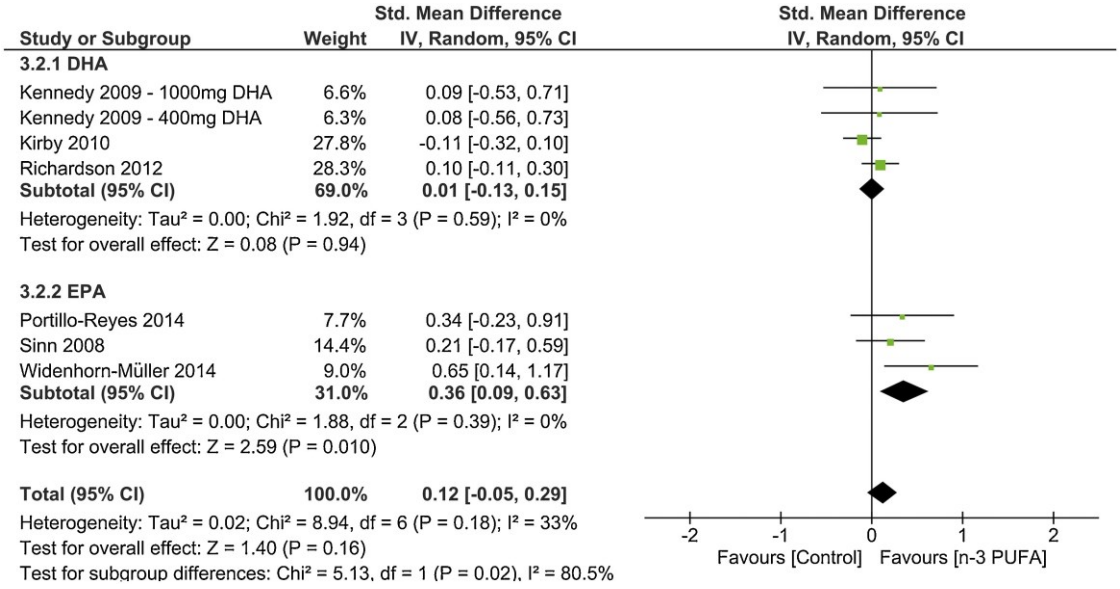
Main treatment effect of n-3 PUFA supplementation on long-term memory (recall) and subgroup analysis for the studies supplementing either more DHA or more EPA.



Note. The horizontal lines represent 95 % CIs, the green square reflects the statistical weight of the study, and its position reflects the SMD for the respective study. The diamond data markers represent overall SMD for subgroup analysis and main treatment effect and 95 % CI's. SMD is standardized mean difference, CI is confidence interval.

Figure 5

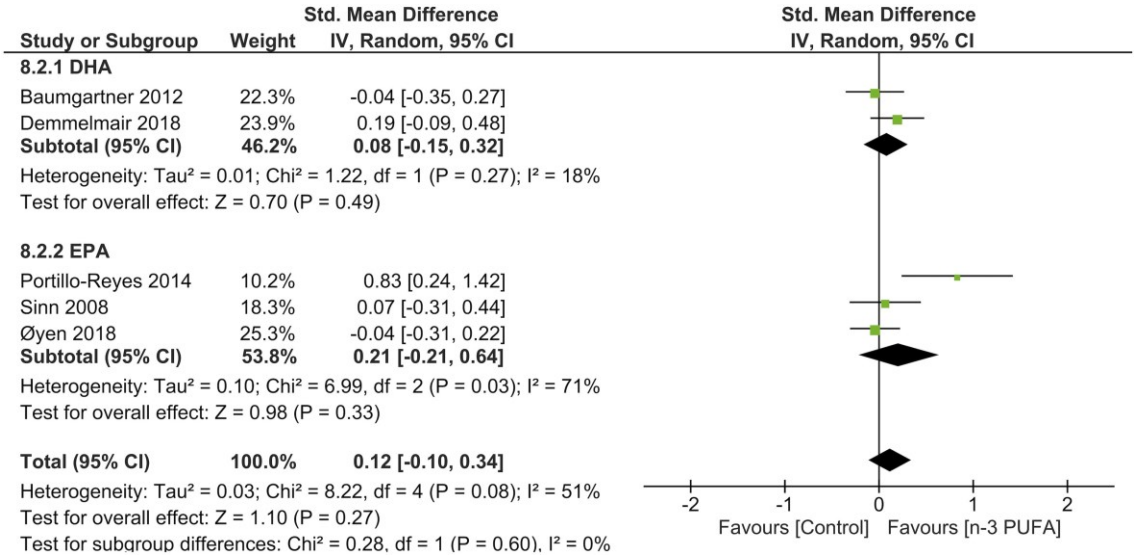
Main treatment effect of n-3 PUFA supplementation on working memory and subgroup analysis for the studies supplementing either more DHA or more EPA.



Note. The horizontal lines represent 95 % CIs, the green square reflects the statistical weight of the study, and its position reflects the SMD for the respective study. The diamond data markers represent overall SMD for subgroup analysis and main treatment effect and 95 % CI's. SMD is standardized mean difference, CI is confidence interval.

Figure 6

Main treatment effect of n-3 PUFA supplementation on problem solving and visuospatial cognition and subgroup analysis for the studies supplementing either more DHA or more EPA.



Note. The horizontal lines represent 95 % CIs, the green square reflects the statistical weight of the study, and its position reflects the SMD for the respective study. The diamond data markers represent overall SMD for subgroup analysis and main treatment effect and 95 % CI's. SMD is standardized mean difference, CI is confidence interval.

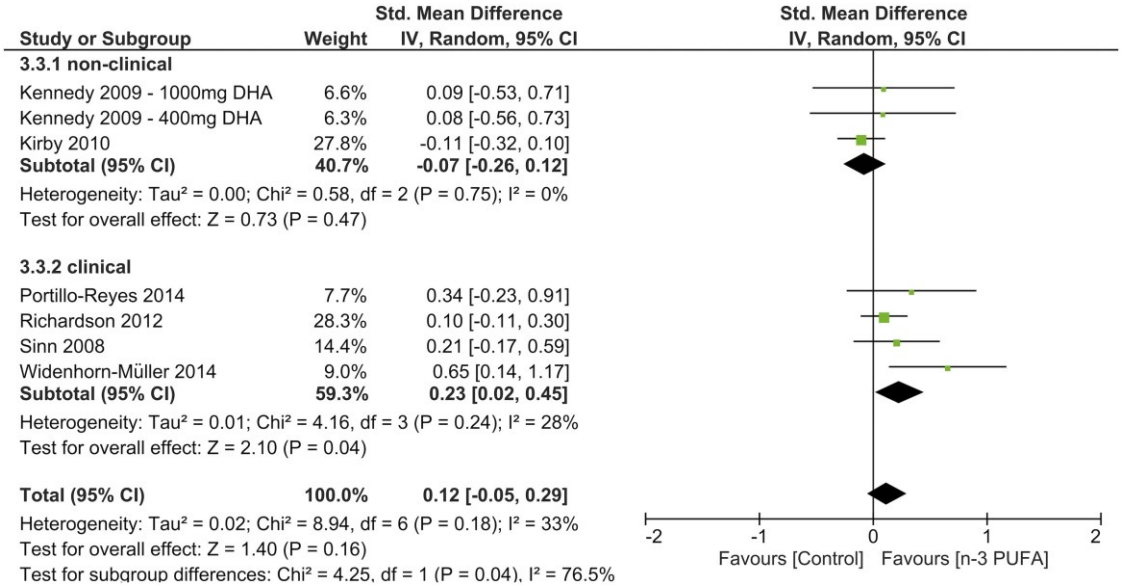
2.3.5 Clinical versus non-clinical populations

Another subgroup analysis was performed for studies with non-clinical participants compared to studies including participants possessing a cognitive deficit or another general health problem. Conversely, small effects were found for the clinical subgroup in the domains of working memory (SMD of 0.23 (95 % CI: 0.02, 0.45)) (Figure 7), shifting and flexibility (SMD of 0.22 (95 % CI: −0.04, 0.48)) (Figure 8), and problem solving and visuospatial cognition (SMD of 0.22 (95 % CI: −0.22, 0.65)) (Figure 9). The analyses on working memory and shifting and flexibility were acceptably heterogeneous (I^2 = 28 %, p = 0.24, I^2 = 36 %, p = 0.18), whereas the analysis on problem solving and visuospatial cognition resulted in a significant percentage of heterogeneity (I^2 = 71 %, p = 0.03). Surprisingly, the analysis resulted in a small effect for the non-clinical subgroup in the domain of long-term memory

(recall) (SMD of 0.22 (95 % CI: −0.15, 0.58)) (Figure 10) with satisfactory heterogeneity (I^2 = 0 %, p = 0.42).

Figure 7

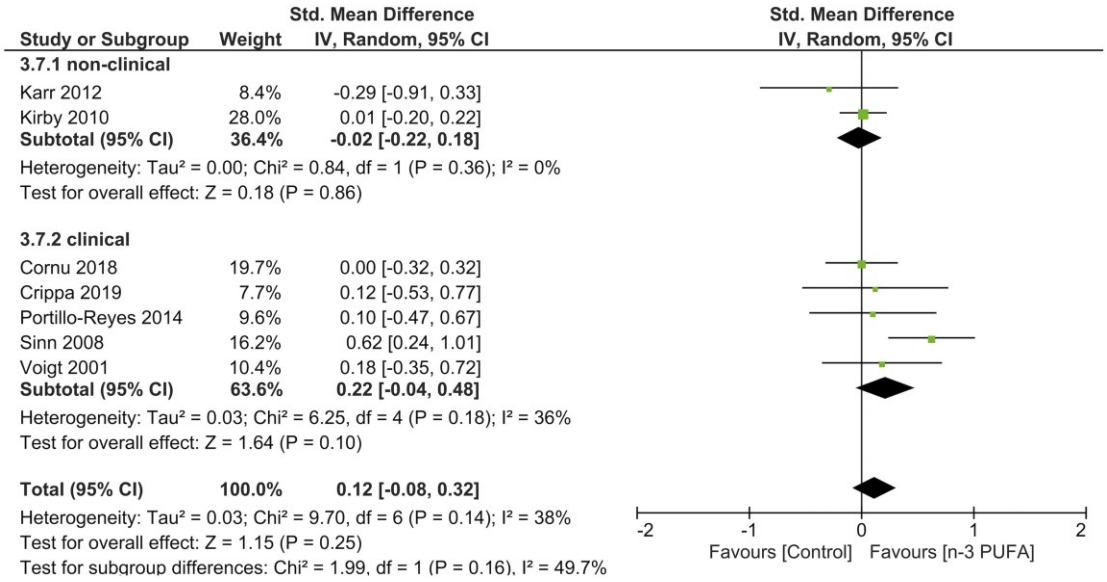
Main treatment effect of n-3 PUFA supplementation on working memory and subgroup analysis for studies supplementing either non-clinical or clinical study populations.



Note. The horizontal lines represent 95 % CIs, the green square reflects the statistical weight of the study, and its position reflects the SMD for the respective study. The diamond data markers represent overall SMD for subgroup analysis and main treatment effect and 95 % CI's. SMD is standardized mean difference, CI is confidence interval.

Figure 8

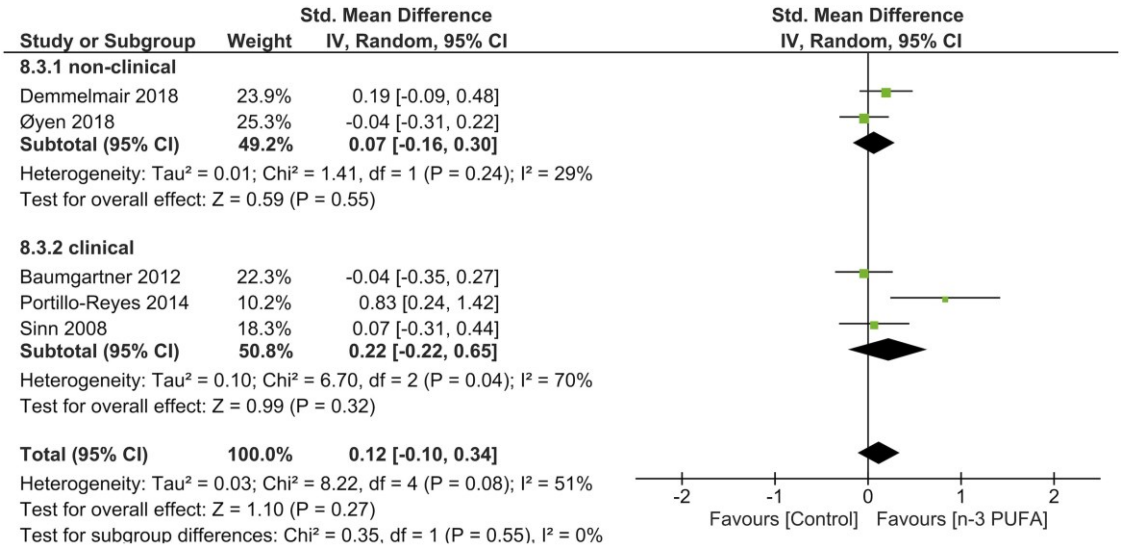
Main treatment effect of n-3 PUFA supplementation on shifting and flexibility and sub-group analysis for studies supplementing either non-clinical or clinical study populations.



Note. The horizontal lines represent 95 % CIs, the green square reflects the statistical weight of the study, and its position reflects the SMD for the respective study. The diamond data markers represent overall SMD for subgroup analysis and main treatment effect and 95 % CI's. SMD is standardized mean difference, CI is confidence interval.

Figure 9

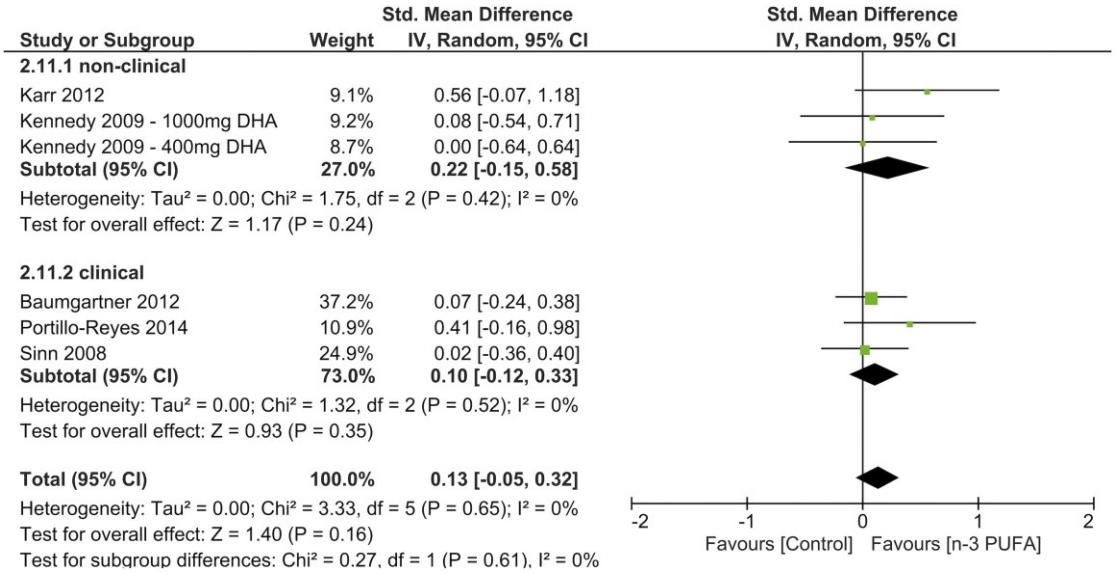
Main treatment effect of n-3 PUFA supplementation on problem solving and visuospatial cognition and subgroup analysis for studies supplementing either non-clinical or clinical study populations.



Note. The horizontal lines represent 95 % CIs, the green square reflects the statistical weight of the study, and its position reflects the SMD for the respective study. The diamond data markers represent overall SMD for subgroup analysis and main treatment effect and 95 % CI's. SMD is standardized mean difference, CI is confidence interval.

Figure 10

Main treatment effect of n-3 PUFA supplementation on long-term memory (recall) and sub-group analysis for studies supplementing either non-clinical or clinical study populations.



Note. The horizontal lines represent 95 % CIs, the green square reflects the statistical weight of the study, and its position reflects the SMD for the respective study. The diamond data markers represent overall SMD for subgroup analysis and main treatment effect and 95 % CI's. SMD is standardized mean difference, CI is confidence interval.

2.3.6 Dose effects

Post exclusion of studies with a daily dose smaller than 400 mg (EPA and DHA combined), the analysis now revealed a small effect size in the domains of both recall and recognition long-term memory with satisfactory heterogeneity (recognition: SMD of 0.24 (95 % CI: −0.12, 0.59), I^2 = 0 %, p = 0.40, recall: SMD of 0.27 (95 % CI: −0.04, 0.58), I^2 = 0 %, p = 0.56)). Owing to this evidence supporting a dose effect, possible dose trends were further investigated. In order to do so, dose trends for the cognitive domains most frequently occurring across the included studies (short-term memory, attention and inhibition), were visualized. EPA and DHA doses were plotted, along with the effect sizes for each of the respective studies. As presented in Appendix D. Fig. 2, Appendix D. Fig. 3 and Appendix D. Fig. 4, no evident dose size trends presented. Furthermore, we performed a correlation analysis for EPA, DHA and n-3 PUFA daily dose with the mean effect size found for each study. Because

the data was not normally distributed, we performed a Spearman's rank correlation. The analysis yielded no significant correlation for neither of the daily dose sizes ($r_s = 0.322$, $p = .089$, $r_s = 0.030$, $p = .878$, $r_s = 0.281$, $p = .140$).

2.3.7 Further analysis of an effect on general cognitive functioning

Although splitting the results into different cognitive domains proved crucial in order to avoid random selection of study results, computing an analysis for general cognitive improvement according to all included studies and domains seemed important. We hence performed a secondary analysis using the best effect reported by each study (Appendix D. Fig. 5). No main effect and no effect in the "more DHA" group presented. However, we again found a small effect for the analysis of the group where more EPA rather than DHA was administered. A detailed overview of the domains and tests included in this analysis and the corresponding SMDs is given in Appendix D. Table 1. Although, for methodological reasons, these results should be interpreted with caution, they support the previously reported differential effects of EPA and DHA, as the analysis might be considered "the largest possible" effect of the two substances.

2.3.8 Sensitivity analysis and asymmetry evaluation

Substantial heterogeneity (>50 %) for main treatment effects was only found for the cognitive domains of problem solving and visuospatial cognition and reading. In order to identify the driver of this heterogeneity, a sensitivity analysis was performed using a random effects model. Heterogeneity dropped from $I^2 = 51$ %, $p = 0.08$ to $I^2 = 0$ %, $p = 0.62$, when data from Portillo-Reyes et al. (2014) was removed from the analysis for problem solving and visuospatial cognition. Also, the SMD dropped from 0.12 (95 % CI: −0.10, 0.34) to 0.04 (95 % CI: −0.11, 0.19), with only four studies left in the meta-analysis. For the domain reading, heterogeneity dropped from $I^2 = 51$ %, $p = 0.06$ to $I^2 = 17$ %, $p = 0.30$, when data from Crippa et al. (2019) was removed. The SMD rose from 0.07 (95 % CI: −0.09, 0.23) to 0.09 (95 %

CI: 0.03, 0.21). We were able to confirm that the specific study data contributed to a significant amount to the heterogeneity in this analysis. However, analysis on the amended datasets did not alter the conclusion about the lack of effect found for these domains.

Asymmetry was assessed using a funnel plot for all domains with more than ten study results in order to look for small study effects. The funnel plot for the domain short-term memory (Appendix D. Fig. 6) and attention (Appendix D. Fig. 7) suggest symmetry, hence providing no evidence for small study effects. The funnel plot for inhibition (Appendix D. Fig. 8) however, seems to suggest some asymmetry. Altogether, the results indicate that biases should be considered when interpreting the results of this meta-analysis.

2.3.9 Moderating variables

In order to investigate possible moderating variables, we tested for significant correlations between year of publication (M = 2009.79, SD = 6.447), duration of supplementation (M = 19.06 weeks, SD = 12.70) and the mean SMD reported for each study over all cognitive domains. As both Shapiro-Wilk and Kolmogorov-Smirnov test confirmed that normal distribution of the data could not be assumed, we performed Spearman's rank correlations. Neither supplementation duration nor year of publication were significantly correlated with mean effect size per study ($r_s = -0.251$, $p = .153$, $r_s = -0.144$, $p = .416$).

2.4 Discussion

In the field of cognitive research, nutrition has been generating considerable interest in terms of its effect on cognitive functioning. Within nutrition research, a growing body of literature has examined possible effects of n-3 PUFA supplementation on cognitive functioning, predominantly due to their key role in the maturation of the brain during gestation (Innis, 2008; Koletzko et al., 2008). As a result of the biological properties of n-3 PUFAs, including their key roles for anti-inflammatory and pro-resolving mediators (Bazinet & Layé, 2014), their

modulatory role in brain development and synaptic plasticity (Layé et al., 2018), their ability to change membrane fluidity (Dyall, 2015) and neurotransmission (Weiser et al., 2016), the role of n-3 PUFAs in promoting cognitive functioning has received considerable critical attention (Luchtman & Song, 2013; Moriguchi, Greiner, & Salem, 2000). Several meta-analyses have attempted to reach a conclusion regarding the cognitive effects of n-3 PUFAs (Abubakari et al., 2014; Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015; Jiao et al., 2014; Mazereeuw et al., 2012), resulting in considerable disagreement. A key problem with much of the literature are the considerable differences between the subjects and intervention products included in the analyses. The aim of the present meta-analysis was to reach a more specific conclusion by addressing shortcomings of previous meta-analyses. More specifically, we excluded studies that administered more AA in the intervention compared to the control group. We also investigated potential differential effects of EPA and DHA on various cognitive domains in children, adolescents and young adults. In addition, we conducted subgroup analyses to determine whether dose size, the cognitive domain tested or the degree of health of study participants (clinical vs. non-clinical) would yield variable results.

2.4.1 Summary of main results

Our analysis combining studies with EPA-rich and DHA-rich n-3 PUFA formulations revealed no main effect of n-3 PUFA supplementation on any cognitive domain. Our subgroup-analysis investigating differential effects of EPA and DHA, identified beneficial effects for EPA-rich formulations in the domains of long-term memory (recall), working memory and problem solving, with high heterogeneity for the latter. However, the computed effects of the meta-analytic data were rather small. DHA-rich formulations had no superior effect over EPA-rich formulations in any cognitive domain. In working memory, shifting and flexibility, and problem solving, clinical populations rather than non-clinical populations benefitted from the intervention, indicating a greater effectiveness of the intervention. Non-clinical par-

ticipants benefitted more than clinical participants in the domain of long-term memory (recall). Removing all data from low dose studies resulted in small effects for long term memory. We were not able to confirm any general dosage effect or trend. Also, no significant correlations were found for daily dose and mean effect size. While including only the results for the domain that yielded the best treatment effects from each study resulted in small but beneficial treatment effects for the EPA group, neither effects for DHA-rich formulations, nor for the combined analysis of EPA- and DHA-rich formulations were observed. This further confirmed our previously described domain-specific results, that indicated a tendency towards a treatment effect of EPA-rich but not DHA-rich formulations. When investigating moderating variables, we found that neither treatment duration nor year of publication were correlated with mean effect size. The sensitivity analysis illustrated that the results reported by Portillo-Reyes et al. (2014) contributed significantly to the heterogeneity found in the analysis on problem solving, and the results reported by Crippa et al. (2019) contributed to the heterogeneity in the domain of reading. However, removing the data from the analysis did not change the conclusion about the lack of a main effect.

2.4.2 Completeness of evidence

A major strength of the current study lies in the broad body of literature that was systematically reviewed with a comprehensive and replicable search strategy. As we encountered only very few disagreements between the two individual literature searches performed and because the studies identified in our study are in line with the ones identified in other meta-analyses, bias in terms of studies that were not identified seems unlikely. However, the exclusion of seven studies due to missing data constitutes a serious drawback.

The protocol heterogeneity observed in studies on n-3 PUFAs and cognition seems to be a key problem with much of the literature on this subject. Because the studies used very different study protocols with large differences in dosage, intervention duration, cognitive tests

and age of participants, finding a consensus on overall treatment effects on cognitive functioning proves challenging. The heterogeneity of study protocols could have a great impact on the statistical evaluation of the treatment effect. However, we succeeded in minimizing this problem by including only test results obtained with standardized cognitive tests rather than questionnaires and most importantly, by clearly separating the results into different cognitive domains to be able to report specific treatment effects. The separation of results into different cognitive domains constitutes a major advantage of this meta-analysis, as it rendered the results interpretable, avoiding the mixture and/or random selection of study results from different cognitive functions. This resulted in a more complete overview of selective effects on different domains, hence also providing results for potentially selective effects in different brain areas. Even more, we were also able to report specific results for clinical and non-clinical youths as well as account for the different PUFA formulations used throughout the different trials (DHA-rich versus EPA-rich formulations). However, this meta-analysis investigated the cognitive effects of n-3 PUFA supplementation in youths only and the conclusions drawn are hence limited to this specific age group. Although we reported results for clinical and non-clinical populations separately, study populations were still quite heterogeneous. The tendency towards an effect in the clinical group adverts to the possibility that supplementation effects on cognition might only be expected in individuals with poor nutritional status or poorer cognitive functioning, as suggested by Chang et al. (2019). Future studies should investigate to what degree nutritional status and baseline cognitive performance contribute to supplementation effects in all study populations investigated.

Based on our findings, we believe that studies investigating cognitive effects of n-3 PUFAs should not pool EPA-rich and DHA-rich formulations in the same meta-analysis. The present meta-analysis provides the framework for further investigations on differential effects of EPA or DHA and different study populations (clinical versus non-clinical populations).

2.4.3 Quality of evidence

All studies included were RCTs with significant methodological quality. We have obtained comprehensive results by selecting only those RCTs that did not administer AA in order to separate n-3 from n-6 PUFA supplementation effects. By including a selective study population, we were able to accurately report treatment effects while brain maturation is still ongoing. We succeeded in eliminating any pre-existing group differences, using change scores instead of only post-treatment scores for most cognitive domains. We also successfully performed a sensitivity analysis, identifying two studies that had great impact on heterogeneity and the associated effects sizes. Additionally, we were able to rule out moderating effects by year of publication and treatment duration by confirming no correlation between these factors and the mean effect sizes.

However, a number of potential shortcomings need to be considered. Although this meta-analysis included 29 studies with 4247 participants, it was limited by the few studies that reported results for a specific cognitive domain, especially in the subgroup analyses. This resulted in statistically sensitive results, highly subject to change should further studies be added. This limitation was confirmed by the finding of one study contributing significantly to the heterogeneity and effect size of one specific cognitive domain. Also, the large confidence intervals supported the conclusion of highly sensitive results.

Furthermore, our risk of bias analysis revealed some considerable flaws in study designs. These could potentially have influenced study results and hence also the results found in this meta-analysis. Risk of bias was nevertheless considered moderate.

Another pitfall lies in the nature of the subgroup analysis performed. Although we established groups where more EPA rather than DHA and vice versa were administered, results generated by this analysis only provide information about the efficacy differences of formulations with different EPA/DHA ratios. Formulations in one group might hence supplement more DHA than EPA and be placed in the DHA group, but still supplement a larger dose of EPA than another study placed in the EPA analysis.

A general limitation lies in the fact that putative moderating variables such as pre- and post-treatment n-3 PUFA blood plasma concentrations were frequently not considered in the included studies or only post hoc and hence could not be included in the meta-analysis. Although participants were randomly allocated to either treatment or control group, it remains unclear whether baseline PUFA levels and compliance might have influenced our study results. Further experimental investigation should therefore determine the effect of pre-treatment levels of n-3 PUFAs, similarly to trials that have investigated how these predict depression outcomes (Carney et al., 2016). Future studies on the current topic should also evaluate possible interactions with other substances and nutrients such as anti-oxidant vitamins (Assmann, Adjibade, Hercberg, Galan, & Kesse-Guyot, 2018) and B vitamins (Jernerén et al., 2019), blood plasma concentration of n-3 PUFAs or more specifically the ApoEε4 allele, as suggested by studies on cognitive decline (Samieri et al., 2011). A related and serious limitation is still the lack of understanding about the actual absorption and utilization of supplemented n-3 PUFAs as well as the influence of the microbiome on PUFA metabolism. Although blood serum levels are a useful measure for intake compliance, it is yet very poorly understood to what extent grey matter or white matter levels change following serum augmentation. It seems to be of great importance, whether the current nutritional status might further influence uptake and utilization of n-3 PUFAs in the human body. More specific studies on n-3 PUFA absorption and moderating factors hence would be invaluable.

2.4.4 Agreements and disagreements with other meta-analyses

In contrast to the meta-analysis conducted by Jiao et al. (2014) we were not able to replicate an overall beneficial effect of n-3 PUFA on cognitive development. This discrepancy may be related to the fact that Jiao et al. (2014) only included studies on the mental development index (MDI). Also, three out of six of their study results within this domain originated from the same study, whereas we were able to include nine study results, all generated by different trials.

Like Cooper et al. (2015) we failed to reveal a main beneficial effect of n-3 PUFA supplementation. Conversely, in line with meta-analyses on depression (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019; Mocking et al., 2016; Sublette, Ellis, et al., 2011), we were able to establish a tendency towards stronger effects of EPA-rich over DHA-rich formulations and stronger effects for clinical than non-clinical populations. These findings are also in line with the results reported by Bloch and Qawasmi (2011) who found moderate effects of n-3 PUFA supplementation on ADHD symptoms especially with higher doses of EPA.

2.5 Author's conclusions

Our meta-analysis of pooled EPA- and DHA-rich n-3 PUFA supplementation was not able to demonstrate an overall effect of n-3 PUFA supplementation on domain-specific cognitive test performance in youths. However, some cognitive domains, in particular long-term memory (recall), working memory and problem solving may benefit from EPA-rich n-3 PUFA formulations. In contrast to EPA-rich formulations, no beneficial effect of DHA-rich formulations could be found, even when only best study effects were considered. We believe that our meta-analysis provides support that it is not justified to combine EPA-rich and DHA-rich formulations in the same meta-analysis. It may in fact well be, that combining the two formulations masks the beneficial neuropsychological effects of EPA-rich formulations.

Nevertheless, to this date, we cannot make clear recommendations about the use of n-3 PUFAs for cognitive enhancement or treatment of cognitive deficits.

Further research should investigate the effects of EPA-rich and DHA-rich n-3 PUFA supplementation separately in order to be able to draw conclusions about differential effects. Most importantly, moderating effects of obesity, inflammatory status, other nutritional components, pre- and post- blood levels of n-3, n-6 and n-9 PUFAs and their interactions with gene variations should be investigated in further detail.

2.6 Appendix – Supplementary material

Appendix A.

Search string: (child OR adolescent OR infant) AND (omega-3 OR PUFA OR EPA OR DHA OR n-3 fatty acid) AND (cognition OR cognitive function OR memory OR attention OR executive function OR verbal fluency OR IQ OR intelligence)

Appendix B.

Risk of bias criteria

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: - Referring to a random number table; - Using a computer random number generator; - Coin tossing; - Shuffling cards or envelopes; - Throwing dice; - Drawing of lots; - Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: - Sequence generated by odd or even date of birth; - Sequence generated by some rule based on date (or day) of admission; - Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: - Allocation by judgement of the clinician;

	- Allocation by preference of the participant; - Allocation based on the results of a laboratory test or a series of tests; - Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT **Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.**	
Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: - Central allocation (including telephone, web-based and pharmacy-controlled randomization); - Sequentially numbered drug containers of identical appearance; - Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: - Using an open random allocation schedule (e.g. a list of random numbers); - Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); - Alternation or rotation; - Date of birth; - Case record number; - Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is

	usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: - No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; - Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: - No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; - Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: - Insufficient information to permit judgement of 'Low risk' or 'High risk'; - The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: - No blinding of outcome assessment, but the review authors judge that

	the outcome measurement is not likely to be influenced by lack of blinding; - Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: - No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; - Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	- Insufficient information to permit judgement of 'Low risk' or 'High risk'; - The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: - No missing outcome data; - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; - For continuous outcome data, plausible effect size (difference in means or standardized difference in

	means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; - Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: - Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; - 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; - Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: - Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); - The study did not address this outcome.
SELECTIVE REPORTING **Reporting bias due to selective outcome reporting.**	
Criteria for a judgement of 'Low risk' of bias.	Any of the following: - The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have

	been reported in the pre-specified way; - The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: - Not all of the study's pre-specified primary outcomes have been reported; - One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; - One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); - One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; - The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS **Bias due to problems not covered elsewhere in the table.**	
Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: - Had a potential source of bias related to the specific study design used; or

	- Has been claimed to have been fraudulent; or - Had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: - Insufficient information to assess whether an important risk of bias exists; or - Insufficient rationale or evidence that an identified problem will introduce bias.

Note. Adapted from the Cochrane Collaboration Risk of Bias Tool. See Higgings & Green (2011) Chapter 8.5: The Cochrane Collaboration's tool for assessing risk of bias.

Appendix C.

Cognitive tests and domains included in quantitative analysis

IQ:

- WISC-III (Osendarp et al., 2007; Sinn et al., 2008)
- WPPSI-III: Total raw score (Demmelmair et al., 2019; Øyen et al., 2018)

Attention:

- KiTAP/TAP: Distractibility: Omission errors (Cornu et al., 2018)
- D2 test of attention: TN-E total performance (Handeland et al., 2017)
- Visual attention factor score (Osendarp et al., 2007)
- Letter cancellation (Portillo-Reyes et al., 2014)
- TOVA: omission errors (Vaisman et al., 2008; Voigt et al., 2001), (Kean et al., 2017) (non-diagnosed subsample, target infrequent, QTR 1))
- Cognitive Drug Research Battery (CDR): Digit Vigilance: Accuracy (%) (Kennedy et al., 2009)
- ANT: focused attention 4 letters – misses (Crippa et al., 2019)

Executive Functions:

Shifting/Flexibility:

- KiTAP/TAP: Flexibility: errors (Cornu et al., 2018)
- TMT-B: completion time: (Karr et al., 2012; Portillo-Reyes et al., 2014)
- TEA-ch: Creature Counting: Trials correct (Sinn et al., 2008), Trials correct age-scaled (Kirby et al., 2010)
- Children's Color Trails Test 2 (Voigt et al., 2001)
- ANT: shifting attentional set – visual: number of errors flexibility (Crippa et al., 2019)

Inhibition:

- KiTAP/TAP: Go/No-go: commission errors (Cornu et al., 2018)
- Stroop Color and Word Test: Interference T-score (Karr et al., 2012), Color-word score (Portillo-Reyes et al., 2014), Stroop score (Sinn et al., 2008)
- Matching Familiar Figures Task (MFFT): number of errors (Kirby et al., 2010)
- CPT-IP: commission errors (McNamara et al., 2010)
- TOVA: commission errors (Kean et al., 2017; Vaisman et al., 2008; Voigt et al., 2001)
- Internet Battery: Arrow Flanker Test : % error (Kennedy et al., 2009)

- ANT: shifting attentional set – visual: number of errors inhibition (Crippa et al., 2019)

Working Memory:

- Working Memory Test Battery for Children (WMTB-C): Backward digit recall (Kirby et al., 2010)
- WISC-IV: Letter-number sequencing (Portillo-Reyes et al., 2014)
- British Ability Scales: Recall of digits backwards (Richardson et al., 2012)
- WISC-III: Digit backwards (Sinn et al., 2008)
- Cognitive Drug Research Battery: Numeric Working Memory: Accuracy (% > chance) (Kennedy et al., 2009)
- HAWIK-IV: Digits backwards (Widenhorn-Müller et al., 2014)

Memory

Short-Term Memory (recall):

- HVLT: recall (J. Baumgartner et al., 2012)
- WISC-III: Digit forward (Sinn et al., 2008)
- RAVLT: Total recall (Karr et al., 2012)
- Working Memory Test Battery for Children (WMTB-C): Forward digit recall (Kirby et al., 2010)
- Verbal learning factor score (Osendarp et al., 2007)
- ENI: verbal immediate recall (Portillo-Reyes et al., 2014)
- British Ability Scales: Recall of Digits Forward (Richardson et al., 2012)
- Cognitive Drug Research Battery (CDR): Immediate word recall (% correct), post-breakfast (Kennedy et al., 2009)
- HAWIK-IV: Digit forward (Widenhorn-Müller et al., 2014)
- Logos Test: Verbal short-term memory (M. Johnson et al., 2017)

Long-Term Memory (recall):

- KABC-II: Atlantis delayed (J. Baumgartner et al., 2012)
- RAVLT: Delayed recall (Karr et al., 2012; Sinn et al., 2008)
- ENI: Free recall (Portillo-Reyes et al., 2014)
- Cognitive Drug Research Battery (CDR): Delayed word recall accuracy: % correct (Kennedy et al., 2009)

Long-Term Memory (recognition):

- HVLT: Delayed recognition (J. Baumgartner et al., 2012)
- ENI: Verbal recognition (Portillo-Reyes et al., 2014)
- RAVLT: Recognition (Sinn et al., 2008)

- Internet Battery: Delayed word recognition (% error), post-breakfast (Kennedy et al., 2009)

Processing speed:

- TMT-A: completion time (Karr et al., 2012; Portillo-Reyes et al., 2014)
- WISC-III: Digit- Symbol Coding (Sinn et al., 2008)
- Children's Color Trails Test 1 (Voigt et al., 2001)
- WPPSI-III: Processing speed raw score (Demmelmair et al., 2019; Øyen et al., 2018)
- ANT: baseline speed (Crippa et al., 2019)

Problem solving and visuospatial cognition:

- KABC-II: Triangles test (J. Baumgartner et al., 2012)
- WISC-IV: Block design (Portillo-Reyes et al., 2014)
- WAIS-III/WISC-III: Block design (Sinn et al., 2008)
- WPPSI-III: Performance (PIQ) raw score (Demmelmair et al., 2019; Øyen et al., 2018)

Language

General language skills:

- ENI: Comprehension instruction (Portillo-Reyes et al., 2014)
- WISC-III: vocabulary subscale (Sinn et al., 2008)
- WPPSI-III: Verbal raw score (VIQ) (Demmelmair et al., 2019; Øyen et al., 2018)
- Internet Battery: Sentence verification: % error (Kennedy et al., 2009)
- Logos Test: Vocabulary (number correct) (M. Johnson et al., 2017)

Reading:

- L'Alouette Test (Cornu et al., 2018)
- WIAT-II Word reading subscale (Kirby et al., 2010)
- WRAT4: Standardized reading score (Parletta et al., 2013)
- NAPLAN: Reading score (Brew et al., 2015)
- Logos Test: Reading comprehension (M. Johnson et al., 2017)
- Wechsler Objective Reading Dimensions (WORD): reading age (Richardson & Montgomery, 2005)
- Battery for the Assessment of Developmental Reading and Spelling Disorders: reading accuracy (Crippa et al., 2019)

Spelling:

- WIAT-II: spelling subscale (Richardson & Montgomery, 2005)

- WRAT4: Standardized spelling score (Parletta et al., 2013)
- Wechsler Objective Reading Dimensions (WORD): spelling age (Richardson & Montgomery, 2005)

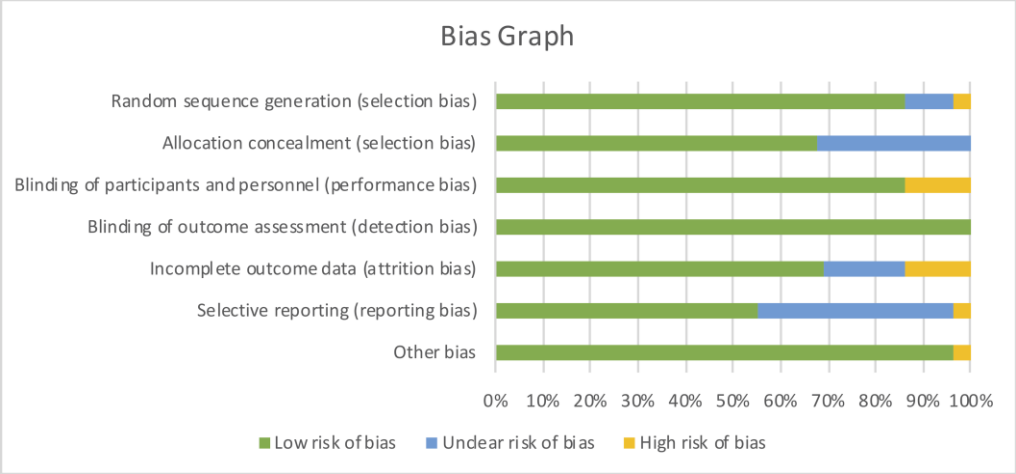
Development:

- Bayley Scales of Infant Development, 2nd edition: MDI (Birch et al., 2000)
- Bayley Scales of Infant and Toddler Development (3rd edition; BSID-III): Cognitive standard score (Meldrum et al., 2012)
- Draw-A-Person (Parletta et al., 2013)
- Bayley Scales of Infant Development: MDI (Makrides et al., 2000; D. T. Scott et al., 1998)
- Willatts' Infant Planning Test: Average total intention score (Van Der Merwe et al., 2013)
- Fagan Test of Infant Intelligence: Novelty preference (%) (Carlson & Werkman, 1996; Werkman & Carlson, 1996)
- Single object free play task: Time on task % (Harbild et al., 2013)

Appendix D. – Figures

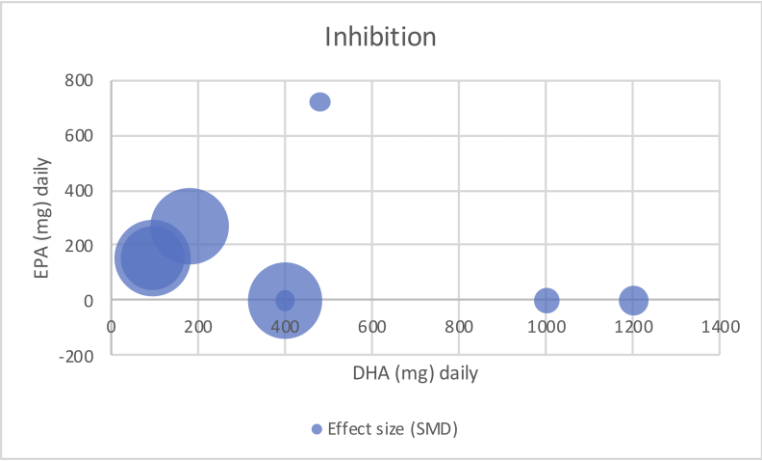
Appendix D. Figure 1

Summary of potential biases across all included studies.



Appendix D. Figure 2

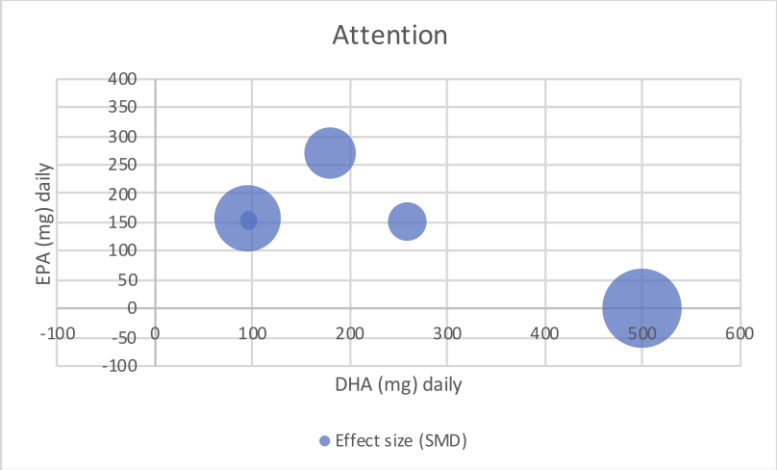
EPA and DHA minimum daily dose size and the corresponding effect sizes found for the studies reporting results for inhibition.



Note. Negative effect sizes and zero effect sizes were omitted from the figure. Negative axis values were added for visualization purposes (bubbles overlapping axes).

Appendix D. Figure 3

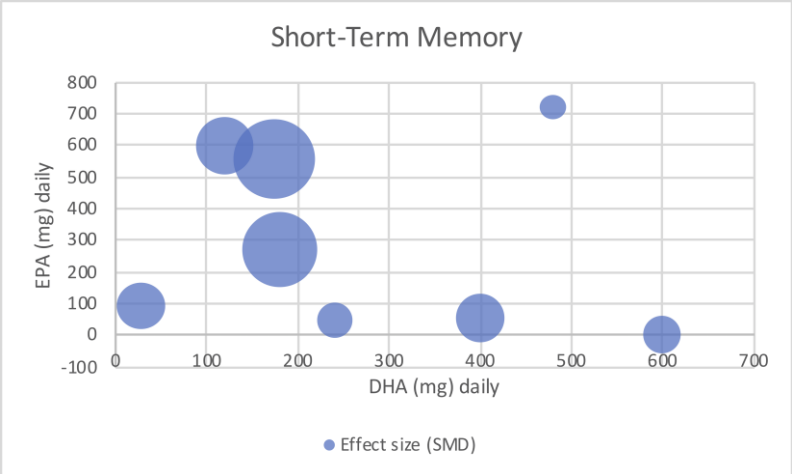
EPA and DHA minimum daily dose size and the corresponding effect sizes found for the studies reporting results for attention.



Note. Negative effect sizes and zero effect sizes were omitted from the figure. Negative axis values were added for visualization purposes (bubbles overlapping axes).

Appendix D. Figure 4

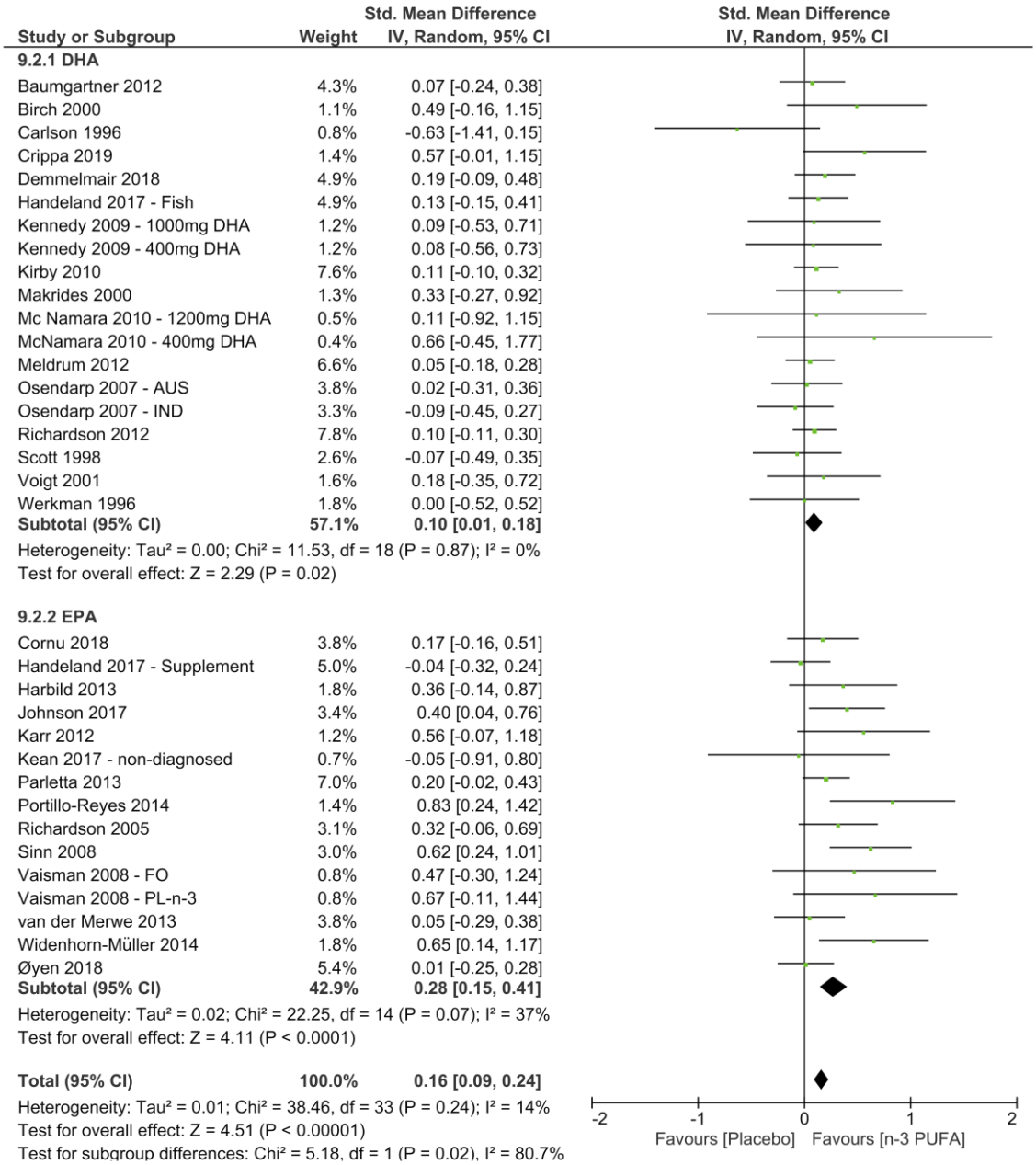
EPA and DHA minimum daily dose size and the corresponding effect sizes found for the studies reporting results for short-term memory.



Note. Negative effect sizes and zero effect sizes were omitted from the figure. Negative axis values were added for visualization purposes (bubbles overlapping axes).

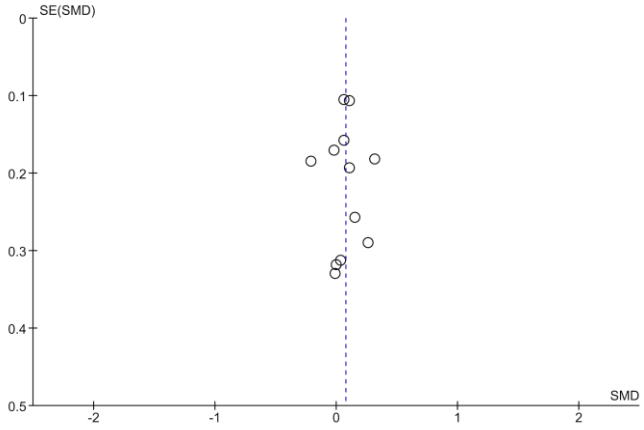
Appendix D. Figure 5

Forest plot of the best results from each study over all cognitive domains.



Appendix D. Figure 6

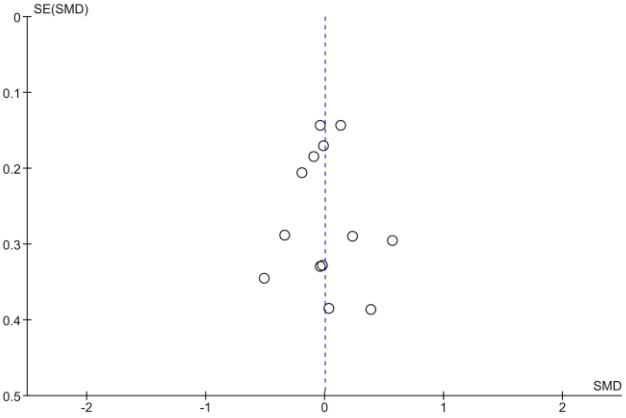
Funnel plot for short-term memory suggesting symmetry.



Note. Bubbles represent the studies reporting results for short-term memory. SMD is standardized mean difference.

Appendix D. Figure 7

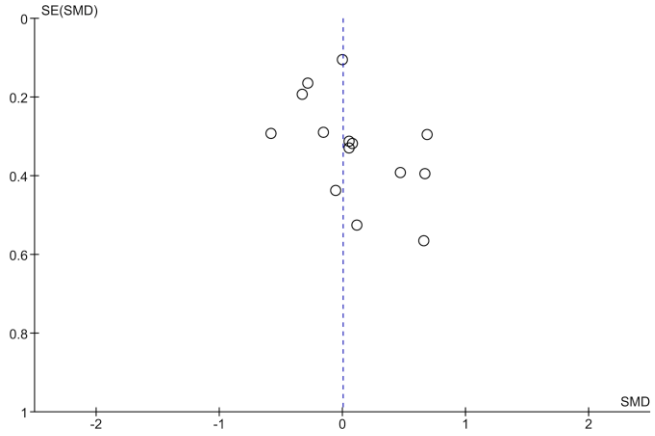
Funnel plot for attention suggesting symmetry.



Note. Bubbles represent the studies reporting results for short-term memory. SMD is standardized mean difference.

Appendix D. Figure 8

Funnel plot for inhibition suggesting some asymmetry.



Note. Bubbles represent the studies reporting results for short-term memory. SMD is standardized mean difference.

Appendix D. – Tables

Appendix D. Table 1

Summary of the largest treatment effects found for each study.

Study	Domain	Test	Effect of intervention	
			SMD	95% CI
Subgroup: DHA				
Mc Namara 2010 – 400 mg DHA	Inhibition	CPT-IP: commission errors	**0.66**	-0.45, 1.77
Crippa 2019	Attention	focused attention 4 letters – misses	**0.57**	-0.01, 1.10
Birch 2000	Development	Bayley Scales of Infant Development, 2nd edition: MDI	**0.49**	-0.16, 1.15
Makrides 2000	Development	Bayley Scales of Infant Development: MDI	**0.33**	-0.27, 0.92
Demmelmair 2018	Problem solving and visuospatial cognition	WPPSI-III: Performance (PIQ) raw score	0.19	-0.09, 0.48
Voigt 2001	Shifting/Flexibility	Children's Color Trails Test 2	0.18	-0.35, 0.72
Handeland 2017 - Fish	Attention	D2 test of attention: TN-E total performance	0.13	-0.15, 0.41
Kirby 2010	Short-term memory	Working Memory Test Battery for Children (WMTB-C): Forward digit recall	0.11	-0.10, 0.32

Appendix D.

Table 1 continued

McNamara 2010 – 1200 mg	Inhibition	CPT-IP: commission errors	0.11	-0.92, 1.15
Richardson 2012	Working Memory	British Ability Scales: Recall of digits backwards	0.10	-0.11, 0.30
Kennedy 2009 – 1000 mg DHA	Working Memory	Cognitive Drug Research Battery: Numeric Working Memory: Accuracy (% > chance)	0.09	-0.53, 0.71
Kennedy 2009 – 400 mg DHA	Working Memory	Cognitive Drug Research Battery: Numeric Working Memory: Accuracy (% > chance)	0.08	-0.56, 0.73
Baumgartner 2012	Long-Term Memory (recall)	KABC-II: Atlantis delayed	0.07	-0.24, 0.38
Meldrum 2012	Development	Bayley Scales of Infant and Toddler Development (3rd edition; BSID-III): Cognitive standard score	0.05	-0.18, 0.28
Osendarp 2007 – AUS	IQ	WISC-III	0.02	-0.31, 0.36
Werkman 1996	Development	Fagan Test of Infant Intelligence: Novelty preference (%)	0.00	-0.52, 0.52
Scott 1998	Development	Bayley Scales of Infant Development: MDI	-0.07	-0.49, 0.35

Appendix D.

Table 1 continued

Osendarp 2007 – IND	Attention	Visual attention factor score	-0.09	-0.45, 0.27
Carlson 1996	Development	Fagan Test of Infant Intelligence: Novelty preference (%)	-0.63	-1.41, 0.15

	n studies[a]	Effects of intervention			Heterogeneity	
		SMD	95% CI	*p*	I^2	*p*
Overall subgroup	19	0.10	0.01, 0.18	0.02	0%	0.87
Subgroup: EPA						
Portillo-Reyes 2014	Problem solving and visuospatial cognition	WISC-IV: Block design			**0.83**	0.24, 1.42
Vaisman 2008 – PL-n-3	Inhibition	TOVA: commission errors			**0.67**	-0.11, 1.44
Widenhorn-Müller 2014	Working Memory	HAWIK-IV: Digits backwards			**0.65**	0.14, 1.17
Sinn 2008	Shifting/Flexibility	TEA-ch: Creature Counting: Trials correct			**0.62**	0.24, 1.01
Karr 2012	Long-term memory	RAVLT: Delayed recall			**0.56**	-0.07, 1.18
Vaisman 2008 – FO	Inhibition	TOVA: commission errors			**0.47**	-0.30, 1.24
Johnson 2017	Reading	Logos Test: Reading comprehension			**0.40**	0.04, 0.76

Appendix D.

Table 1 continued

Harbild 2013	Development	Single object free play task: Time on task	**0.36**	-0.14, 0.87
Richardson 2005	Spelling	WIAT-II: spelling subscale	**0.32**	-0.06, 0.69
Parletta 2013	Development	Draw-A-Person	**0.20**	-0.02, 0.43
Cornu 2018	Reading	L'Alouette Test	0.17	-0.16, 0.51
Van der Merwe 2013	Development	Willatts' Infant Planning Test: Average total intention score	0.05	-0.29, 0.38
Øyen 2018	Processing speed	WPPSI-III: Processing speed raw score	0.01	-0.25, 0.28
Handeland 2017 – Supplement	Attention	D2 test of attention: TN-E total performance	-0.04	-0.32, 0.24
Kean 2017 – non diagnosed	Inhibition	TOVA: commission errors	-0.05	-0.91, 0.80

	n studies[a]	Effects of intervention			Heterogeneity	
		SMD	95% CI	*p*	I^2	*p*
Overall sub-group	15	**0.28**	0.15, 0.41	< 0.0001	37%	0.07
TOTAL	34	**0.16**	0.09, 0.24	< 0.0001	14%	0.24

Note. SMD ≥ 0.20 are marked in bold. [a]Results for different treatment groups were counted as separate studies.

Study 2

Verbal memory performance in depressed children and adolescents: Associations with EPA but not DHA and depression severity

Sophie Emery, Isabelle Häberling, Gregor Berger, Noemi Baumgartner, Michael Strumberger, Mona Albermann, Kristin Nalani, Klaus Schmeck, Suzanne Erb, Silke Bachmann, Lars Wöckel, Ulrich Müller-Knapp, Brigitte Contin-Waldvogel, Bruno Rhiner, Susanne Walitza, Martin Hersberger, Renate Drechsler

This article was originally published in:

Emery, S., Häberling, I., Berger, G., Baumgartner, N., Strumberger, M., Albermann, M., … Drechsler, R. (2020). Verbal Memory Performance in Depressed Children and Adolescents: Associations with EPA but Not DHA and Depression Severity. *Nutrients, 12*(12), 3630. https://doi.org/10.3390/nu12123630

3 Study 2: Verbal memory performance in depressed children and adolescents: Associations with EPA but not DHA and depression severity

Abstract

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been described as positively associated with cognitive functioning. Current meta-analyses have identified eicosapentaenoic acid (EPA) as potentially more effective than docosahexaenoic acid (DHA). An especially vulnerable subgroup that might benefit from these beneficial effects are depressed youths. In this study, we examined associations between red blood cell (RBC) DHA and EPA levels and depression severity and verbal memory performance in a sample of 107 moderately (n = 63) and severely (n = 44) depressed youths. The findings showed that youths with high RBC EPA levels had steeper learning curves compared to those with moderate or low RBC EPA levels (Pillai's Trace = 0.195, p = .027, η_p^2 = .097). No associations between RBC DHA levels or depression severity and verbal memory performance were observed. Our results further confirm previous findings indicating a more important role of EPA compared to DHA in relation to cognitive functioning. Future research should further investigate the differential role of EPA and DHA concerning cognitive functioning in depressed youths. Evidence supporting beneficial supplementation effects could potentially establish a recommendation for a natural and easily accessible intervention for cognitive improvement or remission.

3.1 Introduction

According to the World Health Organization (WHO), approximately 4.4% of the world's population suffer from depression (World Health Organization, 2017), with a lifetime prevalence rate of approximately 10%–15% (Kessler & Bromet, 2013; Kessler et al., 2015). Although the median age of onset lies at around 25 (Kessler & Bromet, 2013), the first symptoms

and onset of depression often occur as early as during childhood or adolescence (Kessler et al., 2007), and earlier onset is associated with poorer health outcomes, such as more depressive episodes, more suicide attempts, and poorer functional outcomes (Zisook et al., 2007). For adolescents, the one-year prevalence rates are estimated to lie around 5% with a large range of approximately 0.2%–17% (Avenevoli et al., 2015; Costello et al., 2005, 2006, 2004). Depression is a very severe mental disorder and can lead to suicide, which, in 2015, was the second leading cause of death amongst 15–29-year-olds (World Health Organization, 2017). In youths, depression has been deemed the leading causes of disability-adjusted life years (DALY) and years lived with disability (YLL) (Erskine et al., 2015). Altogether, these findings highlight the burden that this disease poses on today's youth and the devastating associated consequences.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) defines the diagnostic criteria for major depressive disorder (MDD), which include depressed mood, fatigue, and diminished pleasure, as well as cognitive problems such as difficulties concentrating. To meet the diagnostic criteria for MDD, at least five symptoms must have been present for most of the time during the same two-week period. Symptoms must include either depressed mood or loss of interest or pleasure. In children and adolescents, key symptoms also include irritable mood.

Clinical research to date has primarily focused on the emotional symptoms of depression, while problems with cognition can equally impact everyday functioning and subjective quality of life (Cambridge et al., 2018; Hammar & Årdal, 2009; Knight et al., 2020). Moreover, cognitive deficits have been associated with poorer antidepressant treatment outcome (Bruder et al., 2014; Etkin et al., 2015). Cognitive impairments could be especially problematic when children and adolescents are affected. At this critical stage in life, problems with concentration and cognition could lead to long-lasting consequences concerning personal life and educational attainment (Fletcher, 2008; Morey-Nase et al., 2019). Meta-analyses investigating cognitive deficits in depressed adults have reported moderate impairments in several cognitive domains compared to healthy controls (Ahern & Semkovska, 2017; R. S. C. Lee et

al., 2012; Lim et al., 2013; Porter, Robinson, Malhi, & Gallagher, 2015; Rock et al., 2014; Snyder, 2013; Wagner, Doering, Helmreich, Lieb, & Tadić, 2012). Evidence from several studies suggests that these cognitive problems remain at least partially present even in the remitted stage (Biringer et al., 2007; Bo Jacob Hasselbalch et al., 2011; Semkovska et al., 2019). Although cognitive complaints are equally part of the diagnostic criteria in youths, evidence for impaired cognitive test performance in this subgroup of depressed individuals seems much more heterogeneous. Some meta-analyses have found similar deficits to analyses with adult patients (Brooks, Iverson, Sherman, & Roberge, 2010; Goodall et al., 2018; Wagner et al., 2014). A qualitative review by Vilgis, Silk, & Vance (2015), however, concluded that while some studies reported cognitive deficits in depressed children and adolescents, the majority did not find any impairments. Günther, Holtkamp, Jolles, Herpertz-Dahlmann and Konrad (2004) reported heterogenous results with undisturbed attention, whereas memory impairment was associated with depressive disorders.

In their review, McDermott and Ebmeier (2009) reported negative associations between depression severity and cognitive functioning in adults; however, this effect seemed domain-specific. In youths, thus far only tendencies towards a similar association have been reported (Maalouf et al., 2011), highlighting the need for further investigation into this subject. In the past few years, cognitive remission has become an important goal for MDD treatment; however, treatment options concerning cognitive symptoms are scarce. Evidence for positive cognitive effects of antidepressant medication has proven rather heterogeneous (Bennabi et al., 2019; Biringer et al., 2009; Bortolato et al., 2016; Prado et al., 2018; Rosenblat et al., 2015; Shilyansky et al., 2016; Skandali et al., 2018; Zuckerman et al., 2018).

Since the industrial revolution, nutritional patterns in Western societies have shifted towards foods containing more omega-6 (n-6) compared to omega-3 (n-3) polyunsaturated fatty acids (PUFAs) (Simopoulos, 2011a). These changes have been held responsible for the rise in different civilization diseases such as cardiovascular diseases, but also psychiatric diseases such as depression (Simopoulos, 2011a). n-3 PUFA deficiency has been associated with depres-

sion (Edwards, Peet, Shay, & Horrobin, 1998; F. Li et al., 2015; Lin et al., 2010) and eicosapentaenoic acid (EPA) status has been negatively associated with depression severity (Adams, Lawson, Sanigorski, & Sinclair, 1996). Meta-analytic evidence has further suggested beneficial effects of n-3 PUFA supplementation on depression symptoms (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019; Mocking et al., 2016; Sublette, Ellis, et al., 2011), especially with high doses of EPA (Grosso, Pajak, et al., 2014; Sublette, Ellis, et al., 2011). Interestingly, symptom severity might moderate this beneficial effect, as some studies have reported stronger effects in more severely depressed patients (Appleton et al., 2010). However, other meta-analyses in both adults (Bloch & Hannestad, 2012) and children and adolescents (Zhang et al., 2019) have revealed no beneficial effect of n-3 PUFAs for the treatment of depressive disorder. In youths, however, only four randomized controlled trials (RCTs) thus far have been included (Zhang et al., 2019). The anti-inflammatory properties of n-3 PUFAs have mostly been made responsible for their beneficial effects in relation to depression (Rapaport et al., 2016). Proinflammatory cytokines have been shown to play a role in depression (Young, Bruno, & Pomara, 2014), and hence n-3 PUFAs have been discussed to counteract these inflammatory processes (Bazinet & Layé, 2014).

n-3 PUFAs are vital for normal brain development (J. Baumgartner, 2016; Bazinet & Layé, 2014; Koletzko et al., 2008; Lauritzen et al., 2016). Consequently, the past few years have seen a renewed interest in the investigation of n-3 PUFAs in relation to cognition. Several studies in youths have reported positive associations between reported dietary n-3 PUFA intake and cognitive performance (Darcey, McQuaid, Fishbein, & VanMeter, 2019; Lassek & Gaulin, 2011). In a study by Montgomery, Burton, Sewell, Spreckelsen and Richardson (2013), low blood n-3 PUFA status was associated with poorer reading abilities and working memory performance in children. Similarly, Wurff and colleagues (2016) reported better performance on an attention task for adolescents with higher n-3 PUFA status. Meta-analyses on n-3 PUFA supplementation have reported mixed results, depending on the study population investigated (Abubakari et al., 2014; Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015; Emery et al., 2020; Jiao et al., 2014; Karr, Alexander, & Winningham,

2011; Mazereeuw et al., 2012). It remains unclear whether the specific type of n-3 PUFA ingested might have significantly contributed to these heterogenous study results, as some meta-analyses have suggested beneficial effects of EPA rather than docosahexaenoic acid (DHA) (Chang et al., 2019; Emery et al., 2020).

The question remains as to how n-3 PUFAs might affect cognition in depressed individuals, as supplementation studies in depressed populations are very scarce (Knochel et al., 2015). The results reported by Rogers and colleagues (2008) showed no benefit of n-3 PUFA supplementation on cognition in adult individuals with mild to moderate depression. In youths, however, Vesco, Young, Arnold and Fristad (2018) reported decreased parent-rated impairments in executive functioning after 12-week supplementation with n-3 PUFAs. To the best of our knowledge, there is yet no study investigating associations between EPA and DHA statuses and cognitive performance in depressed children and adolescents.

The aim of the current study was to address the previously mentioned research deficits and to investigate verbal memory performance in depressed children and adolescents in relation to EPA and DHA statuses as well as depression severity. The aforementioned research findings suggest that (1) EPA but not DHA is positively associated with cognitive functioning, (2) depression severity is negatively associated with cognitive functioning, and (3) depression severity might moderate the association between EPA and depression symptoms. We hence hypothesized that patients with a high EPA status would outperform patients with a low EPA status in verbal memory tasks and that this would be especially evident in severely depressed compared to moderately depressed individuals. Furthermore, we hypothesized that moderately depressed patients would outperform severely depressed patients.

If EPA but not DHA were to be identified as being associated with cognitive functioning in depressed children and adolescents, this would prove important, especially for this specific population, as EPA compared to DHA has also been considered to be more effective in the treatment of depression symptoms(Grosso, Pajak, et al., 2014; Sublette, Ellis, et al., 2011). Consequently, future RCTs could investigate EPA supplementation as an intervention in these individuals, targeting both emotional as well as cognitive symptoms at the same time.

3.2 Materials and Methods

The findings reported in this present study were generated from data collected by the "The Omega-3-pMDD trial", a multi-center placebo-controlled trial aiming to investigate the efficacy of omega-3 fatty acid supplementation in moderately to severely depressed children and adolescents aged 8–17 years. Two hundred and twenty patients across Switzerland will be recruited in order to investigate both the psychopathological and cognitive effects of nine months of n-3 PUFA supplementation. In the present study, we report cross-sectional findings from data collected prior to randomization to a treatment arm, with the exception of intellectual ability that was assessed six weeks post-randomization. Funding was received from the Swiss National Foundation and the private foundations that are listed later in the funding section. No industry funding was received. The clinical trial was registered on www.ClinicalTrials.gov, protocol no. NCT03167307. The clinical trial's design paper has already been published (Häberling, Berger, Schmeck, Held, & Walitza, 2019). The study was approved by the local ethics committee and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments. All parents (or legal guardians) provided written informed consent and written or oral assent was obtained from the participating children before entering the study.

3.2.1 Participants

Participants were recruited from seven different in- and outpatient services across Switzerland. For inclusion, the patients had to meet the diagnostic criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (American Psychiatric Association, 2000) and had to have reported symptoms of at least moderate severity defined by a Children's Depression Rating Scale (Poznanski & Mokros, 1996) total score of ≥ 40 (Guo, Nilsson, Heiligenstein, Wilson, & Emslie, 2006). Patients who met the DSM-IV diagnostic criteria for an eating disorder within the last six months or the diagnostic criteria for a lifetime diagnosis of schizophrenia, bipolar affective disorder, or substance dependency were

excluded from the trial. Mental retardation, pervasive development disorder, or pre-existing neurological or medical conditions that are likely to be responsible for depression symptoms constituted further exclusion criteria. Antidepressant treatment was allowed at study entry to avoid selection bias toward less severely depressed patients. Lastly, patients regularly supplementing n-3 PUFAs within the last six months (dosage limit set at 600 mg/day) or patients unable to follow the study procedures (e.g., due to a language barrier) were also excluded.

During the screening visit, inclusion and exclusion criteria were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (Kaufman et al., 1997) and Children's Depression Rating Scale revised (CDRS-R) (Poznanski & Mokros, 1996). Patients meeting all inclusion and no exclusion criteria were then included in the lead-in phase of the trial (7–14 days). During the lead-in phase, all participants received a placebo in a single blinded fashion and psychopathological, cognitive, and bloodwork baseline data were collected. Assessment of the inclusion and exclusion criteria was repeated at the end of this phase, after which patients were randomized to a treatment arm in a double-blind fashion. At the time of analysis, the sample consisted of 107 patients that met all of the inclusion and no exclusion criteria at screening and had analyzed PUFA blood sample data. The current article investigated this subsample in a cross-sectional manner using single cognitive and psychopathological assessments from the lead-in phase of the trial.

3.2.2 Instruments

Sociodemographic variables

Sociodemographic information and information on treatment history were obtained using the patients' medical records, as well as patient and parent interviews. Information on the course of illness was collected via patients' self-reports and parents' reports. The patients' medical records were consulted for confirmation of these reports. Patients or parents provided further information where information was missing or incomplete.

Independent variables

Severity of depression (CDRS-R)

The CDRS-R is a semi-structured clinical interview assessing severity of depression using 17 depression symptoms (Poznanski & Mokros, 1996). Patients and parents provide information on 14 of these symptoms which are then rated on a 7- or 5-point Likert scale, depending on the specific symptom. The interviewer then integrates this information and provides a final score for each symptom. Three further nonverbal symptoms are rated by the interviewer only (depressed facial affect, hypoactivity and listless speech). The final scores for each reported symptom, as well as the ratings on nonverbal symptoms are added up to obtain a final score for depression severity. Scores of 30–39 can be interpreted as mild, 40–59 as moderate, and ≥60 as severe symptoms of depression (Guo et al., 2006). Validation studies on CDRS-R have reported good validity and reliability for depressed children and adolescents (Mayes, Bernstein, Haley, Kennard, & Emslie, 2010).

EPA and DHA Statuses

Venous blood samples were collected. For determination of erythrocyte fatty acid composition, blood was drawn into EDTA tubes, centrifuged, and then the plasma and buffy coat taken off; the erythrocytes were then frozen at −80 °C until analysis. The fatty acid composition of the erythrocytes was analyzed by gas chromatography at Omegametrix GmbH using previously described methods (Harris et al., 2013). EPA and DHA statuses are given as a percentage of total fatty acids measured in RBCs.

Outcome Variables

Cognitive Tests - Memory

Verbal memory: VLMT

We used a validated German version (Verbaler Lern- und Merkfähigkeitstest (VLMT) (Helmstaedter & Durwen, 1990)) of the Auditory Verbal Learning Test (AVLT) (Schmidt,

1996a), in which a list of 15 semantically independent words is presented auditorily to an individual and he or she is asked to remember and reproduce as many words as possible. This process is repeated five times. Then, a second list of 15 words (= interference list (I)) is presented and the individual is asked to remember and reproduce as many words as possible from the second list. In the next step, the individual is asked to reproduce the words from the first list. After 20–30 min, he or she is once again asked to reproduce the first list of words. In the last step, the individual is asked to recognize the words from a list of 50 semantically or phonetically related and unrelated words. The test measures declarative verbal memory capacity. Short-term verbal memory is characterized by the number of words correctly reproduced by the individual in each of the five rounds (T1, T2, T3, T4, and T5). The long-term memory parameters are T7, which is the number of words from the first list recalled after 20–30 min, and T5–T7, which is the difference between the number of words recalled at T5 and T7. The interference score is I, which represents the number of correctly reproduced words from the interference list, T6, which is the number of words from the first list recalled after interference, and T5–6, which is the difference between the number of words reproduced from the first list before and after interference. Lastly, recognition (W) is the number of words correctly identified as belonging to the first list, and W–F is the correctly identified words minus the words wrongly attributed to the first list.

Numeric memory: WISC-IV digit span

The digit span subtest from the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV) (Wechsler, 2003) consists of two parts, namely, forward and backward. In the first part, the individual has to reproduce sequences of digits of increasing length. In the second part, the individual is instructed to repeat a sequence of digits in reverse order. The test measures numeric short-term memory and working memory.

Control Variables

IQ: Reynolds Intellectual Assessment Scales and Screening (RIAS)

The RIAS is an intelligence test for individuals between 3 and 99 years of age, mostly used for research purposes (Hagmann-von Arx & Grob, 2014). It includes two subtests, the results of which are added to form a verbal intelligence index (VIX) and two subtests to form the nonverbal intelligence index (NIX). These are then integrated into the global intelligence index (GIX). Reliability of the RIAS is high (Cronbach $\alpha = 0.95$ for the global index) (Gygi, Hagmann-von Arx, Schweizer, & Grob, 2017; Krist, Kunter, Nückles, Pinquart, & Seidel, 2016).

C-reactive protein (CRP)

High-sensitive CRP was measured in the plasma in an accredited medical laboratory using a commercial assay with a coefficient of variation of 1.3% at 3.6 mg/L, to be used as a marker for low-grade inflammation and as a stratification parameter for randomization. Values above 10 were excluded from analysis, as they could have indicated infection.

Body-mass-index (BMI)

The BMI was calculated using weight (kg)/height $(cm)^2$. BMI was not obtained in some cases because of missing measurement tools and devices.

3.2.3 Statistical analysis

Statistical Package for the Social Sciences (SPSS) software version 26 was used for all statistical analyses. Descriptive statistics are given in order to describe the study sample characteristics. Moderately and severely depressed patient groups were distinguished using a clinical cut-off of the CDRS-R total score (40–59 = moderate; ≥60 = severe) (Guo et al., 2006). Three approximately equally sized groups were formed according to the data distribution of EPA and DHA statuses, because patient's n-3 PUFA statuses were all low when referring to

currently proposed ideal levels (von Schacky, 2019a). Hence, the formation of three groups would allow for the investigation of especially low status and rather normal values. Differences between moderately and severely depressed patients and differences between EPA and DHA status groups for the investigation of potential confounding variables were analyzed using chi-square tests, independent t-tests, and one-way ANOVAs, depending on the scale level of the variable investigated. Non-parametric Mann–Whitney *U* or Kruskal–Wallis tests were only used for strongly skewed data (>1, <(−1)), as in large sample sizes parametric tests should be robust against the violation of normality assumption (Lumley, Diehr, Emerson, & Chen, 2002).

In order to investigate differences in memory scores depending on depression severity (moderate vs. severe) and EPA and DHA statuses (low, intermediate, and high), multivariate analyses of covariance (MANCOVAs) were computed to evaluate the VLMT short-term, long-term, and interference parameters separately. Multivariate outliers were checked using Mahalanobis' distances. Bonferroni correction was applied for the interpretation of between-subjects effects and pairwise comparisons. For digit span parameters, univariate analyses of covariance (ANCOVAs) were used for the forward and backward parameters separately.

Conservative results using Pillai's Trace instead of Wilk's Lambda were reported (Ateş, Kaymaz, Kale, & Tekindal, 2019). Pillai's Trace values range from 0 to 1 with increasing values indicating a stronger contribution of the independent variable to the model. For all MANCOVAs, normal distribution within groups was investigated using Shapiro–Wilk tests and Q-Q plots where $n \leq 25$. Box's tests were used to evaluate the homogeneity of variance–covariance matrices. Levene's tests were used to assess the equality of error variances, although the results should be robust against violation if none of the standard deviations are more than four times as large as the corresponding smallest standard deviation (Howell, 2012). The homogeneity of regression slopes was assessed for all covariates. Significance levels were set at $p < 0.05$.

3.3 Results

At the time of analysis, the subsample of patients that met all inclusion and no exclusion criteria and where blood samples were available consisted of 107 patients. For one patient, the WISC digit span scores were missing due to the fact that the test had not been done with this individual. RIAS scores for seven patients were missing, because IQ testing was done six weeks post-randomization and these patients had not yet reached week six of the study.

3.3.1 Descriptive statistics

Patients achieved average mean normative scores for both the VLMT total learning parameter (ΣT-15) (T-score, M = 49.15, SD = 9.21) as well as the WISC digit span score (scaled score metric, M = 9.57, SD = 2.43). However, a significant proportion of patients achieved below average scores, with 24 patients (22.42%) with T-scores < 40 for the VLMT; moreover, 24 patients (22.64%) achieved scaled metric scores < 8 for the digit span test. There was one outlier for long-term memory scores, with a Mahalanobis' distance of 25.72 (critical value = 13.82); however, it was decided not to exclude this participant because all other memory parameters were within normal range. Only 5.8% achieved recognition normative scores below average and 67% recognized all 15 words from the list. The skewness of the recognition data was -2.32 (SE = 0.23) and kurtosis was 6.51 *(*SE = 0.47). A total of 46.2 % of the participants reached maximum recognition scores even when subtracting interference or false positive mistakes (skewness -1.691 (SE = 0.25) and kurtosis 2.96 (SE = 0.47)). Hence, it was decided to investigate depression severity and EPA/DHA group differences concerning recognition scores using nonparametric Kruskal-Wallis tests and Mann-Whitney U test instead of MANCOVAs.

Severity group formation resulted in a group of 63 moderately depressed patients and a group of 44 severely depressed patients. The sociodemographic information, IQ, physiological parameters and psychopathology data are summarized in Table 8 for both severity groups. Severely depressed patients were over proportionally female compared to moderately depressed

patients; hence, gender was later entered as a covariate for ANCOVA and MANCOVA analyses. No other group differences except CDRS-R score differences presented between severity groups. Importantly, no differences concerning antidepressant use were found.

Table 8.

Descriptive statistics for sociodemographic information, biological parameters, IQ, psychopathology

Sample Characteristics	**Variable Specifics**	***n***	***M (SD)***	**Min**	**Max**	**Moderate depression** ***M (SD)***	**Severe depression** ***M (SD)***	$t/\chi^2/U$	***p***
Sociodemographic information	Age	107	15.50 (1.89)	8.67	18.00	15.25 (2.09)	15.85 (1.51)	-1.630	.106
	Sex: %female	107	67%			57%	82%	7.166	.007**
Physiological parameters	BMI	99	22.35 (4.87)	14.00	39.80	21.86 (4.35)	23.06 (5.52)	1285.0	.454
	CRP	105	0.79 (1.26)	0	6.6	0.65 (0.81)	0.99 (1.69)	1220.0	.410
IQ									
RIAS	VIX	100	101.73 (9.93)	79	129	102.58 (10.18)	100.51(9.61)	1.019	.102
	NIX	100	106.33 (8.93)	70	123	107.71 (8.61)	104.34 (9.12)	1.879	.310
	GIX	100	104.52 (9.35)	76	128	105.78 (9.32)	102.68 (9.21)	1.651	.102
Depression severity									
CDRS-R	Total score	107	57.73 (7.76)	42	79	52.37 (4.18)	65.41 (4.54)	- 15.331	<.001***
	aSevere %	44	41.1%			-	-	-	-
Course of illness									
Mean duration of depression (months)	Months	104	14.71 (11.69)	1	84	13.45 (9.76)	16.43 (13.84)	1503.0	.228

Table 8 continued									
Total number of episodes		105	1.46 (0.95)	1	8	1.44 (1.10)	1.48 (0.70)	1490.0	.230
Recurrent depression	Yes	104	31%			26%	38%	1.775	.183
Use of antidepressant medication	Yes	102	37%			35%	40%	0.317	.573

Note. $^{**}p < .01$, $^{***}p < .001$. CRP, C-reactive protein, BMI, body mass index, VIX, verbal intelligence index, NIX, nonverbal intelligence index, GIX, global intelligence index, RIAS, Reynolds Intellectual Assessment Scales and Screening, CDRS-R, Children's Depression Rating Scale revised. [a]CDRS-R severity scores: 40-59 = moderate, ≥ 60 = severe

EPA group formation resulted in three groups (n_1 = 34, n_2 = 39, n_3 = 34) with group means of M_1 = 0.34 (*SD* = 0.05), M_2 = 0.46 (*SD* = 0.04), M_3 = 0.66 (*SD* = 0.11). No gender (χ^2 = 0.172, p = .918), age ($F(2,104) = 0.816$, p = .445), IQ ($F(2,97) = 2.317$, p = .104), BMI ($H(2)$ = 2.950, p = .229), CRP ($H(2)$ = 2.771, p = .250) or differences concerning antidepressant use (χ^2 = 0.866, p = 0.649) presented between the three groups. DHA group formation resulted in three groups (n_1 = 36, n_2 = 35, n_3 = 36) with group means of M_1 = 2.89 (*SD* = 0.22), M_2 = 3.48 (*SD* = 0.20), M_3 = 4.54 (*SD* = 0.61). Moreover, between these groups, no gender (χ^2 = 0.468, p = .791), age ($F(2,104) = 0.774$, p = .464), IQ ($F(2,97) = 0.924$, p = .401), ($H(2)$ = 0.987, p = 0.611), CRP (H(2) = 0.539, p = .764) or differences concerning antidepressant use (χ^2 = 0.527, p = .768) were found.

As shown in Table 9, severely depressed patients had higher DHA and total omega-3 status compared to moderately depressed patients. No significant differences concerning EPA status were observed.

Table 9

Fatty acid status for moderately and severely depressed patients

	Total	Moderate MDD (*n*=63)	Severe MDD (*n*=44)	*t*	*p*
Fatty acid	*M (SD)*	*M (SD)*	*M (SD)*		
EPA	0.49 (0.15)	0.47 (0.14)	0.51 (0.16)	-1.515	.133
DHA	3.63 (0.79)	3.50 (0.71)	3.82 (0.87)	-2.077	.040*
All n-6	34.37 (1.32)	34.45 (1.26)	34.32 (1.40)	0.512	.609
All n-3	6.45 (1.0)	6.26 (0.93)	6.71 (1.06)	-2.318	.022*
AA/EPA	35.10 (11.27)	36.08 (11.21)	33.74 (11.60)	1.045	.298

Note. *p < .05. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n-6, omega-6; n-3, omega-3; AA, arachidonic acid.

3.3.2 Main analysis – EPA status and depression severity in relation to memory

The MANCOVA results for short-term memory VLMT parameters resulted in a significant main effect for EPA status ($F(10,194) = 2.094$, $p = .027$) but not for depression severity ($F(5,96) = 0.622$, $p = .684$). The between-subjects effects of EPA status were significant for the second trial (T2) ($F(2,100) = 6.096$, $p = .003$) and reached borderline significance for T3 ($F(2,100) = 4.825$, $p = .010$) after Bonferroni correction of significance level ($p < .01$). Pair-wise comparisons showed that patients with a high EPA status ($M = 10.96$, $SE = 0.37$) out-performed patients with a moderate ($M = 9.42$, $SE = 0.35$, $p = .009$) or low ($M = 9.32$, $SE = 0.40$, $p = .010$) EPA status in T2. The same results presented for T3, where patients with a high EPA status ($M = 12.23$, $SE = 0.35$) outperformed patients with a moderate ($M = 10.97$, $SE = 0.33$, $p = .027$) or low EPA status ($M = 10.86$, $SE = 0.37$, $p = .023$). The VLMT short-term memory score profiles for the three EPA status groups are shown in Figure 11. The results indicate that patients with a high EPA status had steeper learning curves compared to those with a moderate or low EPA status. No main effect of either EPA status or depression severity presented for interference, long-term memory parameters, and the parameters of the digit span test. All results are summarized Table 10. Independent samples Kruskal-Wallis test showed no effect of EPA status for either the uncorrected ($H(2) = 0.893$, $p = .640$) or the corrected recognition parameter ($H(2) = 2.239$, $p = .326$); there was also no significant effect of depression severity ($U = 1370.500$, $p = .901$, $U = 1274.000$, $p = .580$). Further analyses concerning potential confounding group differences revealed no significant IQ differences between the six EPA/severity groups.

Table 10

MANCOVA and ANCOVA results for VLMT and digit span parameters. EPA status and depression severity entered as factors and gender as a co-variate.

			MANCOVA EPA status (EPA) Depression severity (S) Interaction Severity*EPA status (I) Covariate: Gender (G)					
VLMT short-term memory parameters			**EPA: $F(10,194) = 2.094$, $p = .027$*, $\eta_p^2 = .097$** S: $F(5,96) = 0.622$, $p = .684$, $\eta_p^2 = .031$ I: $F(10,194) = 0.910$, $p = .525$, $\eta_p^2 = .045$ G: $F(5,96) = 1.287$, $p = .276$, $\eta_p^2 = .063$					
	Moderate depression $N = 63$ *M* (*SD*)	Severe depression $N = 44$ *M* (*SD*)	*F* *p* η_p^2				Pairwise	*p*
			EPA	S	I	G		
T1 score								
Low EPA	6.52 (0.33)	6.55 (0.53)	1.044	0.816	0.415	0.600	NS	NS
Moderate EPA	7.00 (0.35)	6.29 (0.46)	.356	.369	.661	.440		
High EPA	7.11 (0.40)	7.06 (0.42)	.020	.008	.008	.006		
T2 score								
Low EPA	9.74 (0.52)	8.91 (0.69)	**6.096**	1.577	2.030	0.000	EPA: h > m	$p = .009$**
Moderate EPA	10.14 (0.56)	8.71 (0.46)	**.003***	.212	.137	.997	EPA: h > l	$p = .010$*
High EPA	10.67 (0.26)	11.25 (0.44)	**.109**	.016	.039	.000		
T3 score								
Low EPA	11.43 (0.40)	10.36 (0.64)	**4.825**	1.674	1.366	2.470	EPA: h > m	$p = .027$*
Moderate EPA	11.27 (0.52)	10.71 (0.45)	**.010°**	.199	.260	.119	EPA: h > l	$p = .023$*
High EPA	11.94 (0.38)	12.50 (0.52)	**.088**	.016	.027	.024		

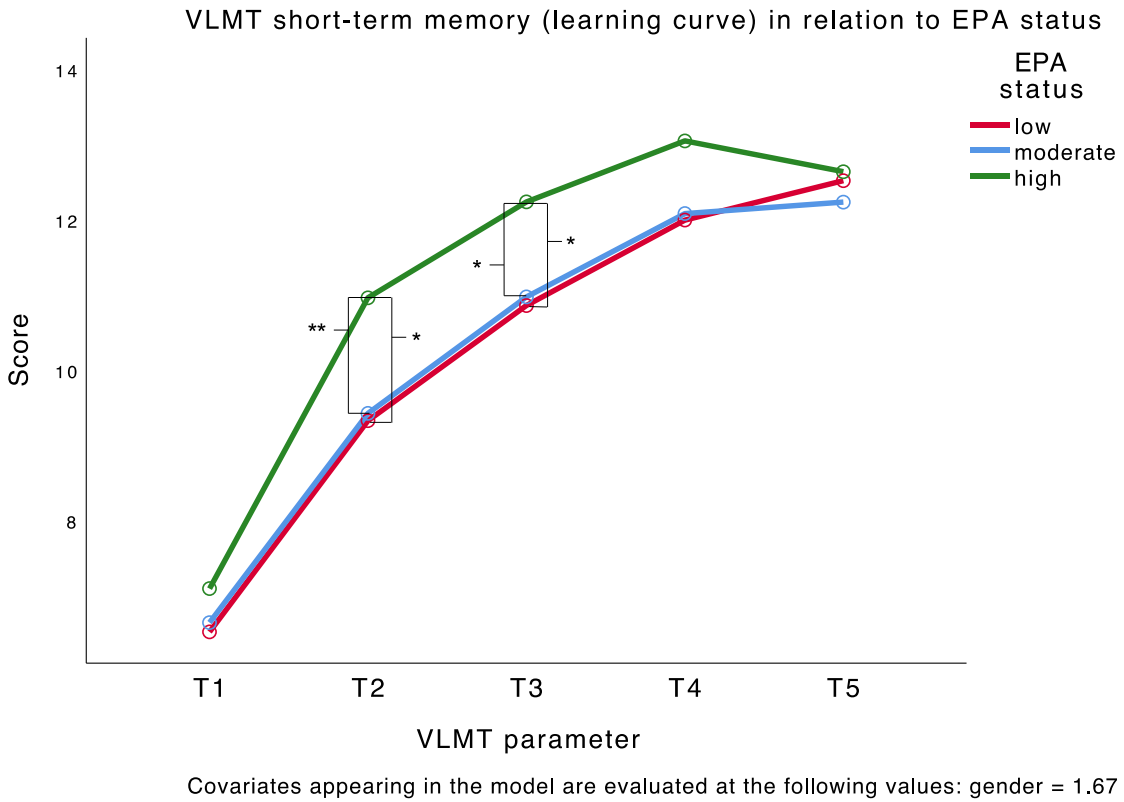
Table 10 continued								
T4 score								
Low EPA	12.17 (0.38)	10.91 (0.64)	2.652	0.944	0.082	3.069	NS	NS
Moderate EPA	12.32 (0.50)	11.88 (0.70)	.075	.334	.921	.083		
High EPA	13.00 (0.33)	13.06 (0.42)	.050	.009	.002	.030		
T5 score								
Low EPA	12.57 (0.38)	12.55 (0.51)	0.410	0.103	0.059	2.101	NS	NS
Moderate EPA	12.32 (0.50)	12.18 (0.58)	.665	.749	.942	.150		
High EPA	12.50 (0.41)	12.75 (0.37)	.008	.001	.001	.021		
VLMT interference parameters	EPA: $F(6,198) = 1.426$, $p = .206$, $\eta_p^2 = .041$ S: $F(3,98) = 1.056$, $p = .372$, $\eta_p^2 = .031$ I: $F(6,198) = 0.102$, $p = .996$, $\eta_p^2 = .003$ G: $F(3,98) = 0.869$, $p = .460$, $\eta_p^2 = .026$							
I								
Low EPA	6.43 (0.40)	6.18 (0.62)	1.671	2.280	0.079	1.414	NS	NS
Moderate EPA	6.41 (0.44)	5.71 (0.58)	.193	.134	.924	.237		
High EPA	7.33 (0.71)	6.63 (0.52)	.032	.022	.002	.014		
T6								
Low EPA	11.96 (0.59)	11.55 (0.56)	2.364	0.680	0.134	1.917	NS	NS
Moderate EPA	11.36 (0.56)	10.94 (0.70)	.101	.411	.875	.169		
High EPA	12.28 (0.43)	12.44 (0.48)	.045	.007	.003	.019		
T5-6								
Low EPA	0.61 (0.43)	1.00 (0.54)	2.556	0.756	0.075	0.107	NS	NS
Moderate EPA	0.95 (0.24)	1.24 (0.36)	.083	.387	.928	.744		
High EPA	0.22 (0.31)	0.31 (0.37)	.049	.008	.001	.001		
VLMT long-term memory parameters	EPA: $F(4,200) = 0.604$, $p = .660$, $\eta_p^2 = .012$ S: $F(2,99) = 0.055$, $p = .946$, $\eta_p^2 = .001$ I: $F(4,200) = 0.093$, $p = .984$, $\eta_p^2 = .002$ G: $F(2,99) = 1.123$, $p = .330$, $\eta_p^2 = .022$							

Table 10 continued								
T7								
Low EPA	11.78 (0.54)	11.82 (0.48)	1.100	0.091	0.157	1.832	NS	NS
Moderate EPA	11.55 (0.67)	11.18 (0.69)	.337	.763	.855	.179		
High EPA	12.00 (0.46)	12.44 (0.58)	.022	.001	.003	.001		
T5-7								
Low EPA	0.78 (0.36)	0.73 (0.41)	0.774	0.007	0.123	0.128	NS	NS
Moderate EPA	0.77 (0.44)	1.00 (0.39)	.464	.934	.884	.721		
High EPA	0.50 (0.31)	0.31 (0.44)	.015	.000	.002	.001		
Digits forward								
Low EPA	8.68 (0.44)	8.64 (0.41)	0.654	0.018	0.019	0.043	NS	NS
Moderate EPA	8.45 (0.37)	8.29 (0.49)	.522	.894	.981	.837		
High EPA	8.89 (0.40)	8.88 (0.52)	.013	.000	.000	.000		
Digits backwards								
Low EPA	8.09 (0.41)	7.64 (0.49)	0.556	1.016	0.188	0.151	NS	NS
Moderate EPA	8.41 (0.47)	7.88 (0.36)	.575	.316	.829	.699		
High EPA	8.33 (0.43)	8.31 (0.27)	.011	.010	.004	.002		

Note: η_p^2= .01 (small), .06 (medium), .14 (large). l, low EPA; m, moderate EPA; h, high EPA. Group sizes (n): Moderately depressed with a low EPA status = 23; moderately depressed with a moderate EPA status = 22; moderately depressed with a high EPA status = 18; severely depressed with a low EPA status = 11; severely depressed with a moderate EPA status = 17; severely depressed with a high EPA status = 16. Multivariate effects, pairwise comparisons: °borderline significant *$p < 0.05$, **$p < 0.01$. Between-subjects effects: °borderline significant, *$p < .010$ (short-term memory), *$p < .017$ (interference), *$p < .025$ (long-term memory) after Bonferroni correction of significance level. Significant effects are marked in bold. T1-7, trials 1-7; NS, not significant.

Figure 11

VLMT learning curve in relation to EPA status.



Note. N = 107. *$p < 0.05$, **$p < 0.01$

3.3.3 Main analysis – DHA status and depression severity in relation to memory

The same analyses were run using DHA instead of EPA status as a factor. A significant interaction effect for long-term memory parameters was found ($F(4,200) = 3.069$, $p = .018$). However, in contrast to the EPA analyses where no IQ differences were found between the groups, further analyses revealed significant IQ differences between moderately and severely depressed patients in the moderate DHA status group. Moderately depressed patients had significantly higher GIX scores ($M = 106.05$, $SD = 8.56$) compared to severely depressed patients in the moderate DHA status group ($M = 97.62$, $SD = 10.57$; $t(31) = 2.537$, $p = .016$). Hence, the MANCOVA and ANCOVA analyses were rerun entering IQ as a second covariate. A significant main effect for DHA status was found for digits forward scores ($F(2,91) =$

3.342, $p = .040$). However, pairwise comparisons were no longer significant after Bonferroni correction for multiple comparisons. No significant main effect for depression severity presented for any memory parameter. A borderline significant interaction effect presented for interference parameters of the VLMT $F(6,182) = 2.219$, $p = .052$). Between-subjects effects revealed a significant effect for the T6 parameter $F(2,92) = 4.337$, $p = .016$) where severely depressed patients with a high DHA status ($M = 12.56$, $SE = 0.50$) outperformed severely depressed patients with a moderate DHA status ($M = 10.50$, $SE = 0.61$, $p = .036$). Moreover, in the moderate DHA status group, moderately depressed patients ($M = 12.34$, $SE = 0.47$) outperformed severely depressed patients ($M = 10.50$, $SE = .061$, $p = .021$). IQ proved a significant covariate for nearly all parameters. All MANCOVA and ANCOVA results are summarized in Table 11. Independent samples Kruskal-Wallis test showed no effect of DHA status for either the uncorrected ($H(2) = 0.522$, $p = .770$) or the corrected recognition parameter ($H(2) = 2.054$, $p = .358$).

Table 11

MANCOVA and ANCOVA results for VLMT and digit span parameters.

			MANCOVA DHA status (DHA) Depression severity (S) Interaction Severity*DHA status (I) Covariates: Gender (G), GIX (IQ)						
VLMT short-term memory parameters			DHA: $F(10,178) = 1.323$, $p = .221$, $\eta_p^2 = .069$ S: $F(5,88) = 0.524$, $p = .758$, $\eta_p^2 = .029$ I: $F(10,178) = 0.686$, $p = .736$, $\eta_p^2 = .037$ G: $F(5,88) = 1.218$, $p = .308$, $\eta_p^2 = .065$ **IQ: $F(5,88) = 6.113$, $p < .001$***, $\eta_p^2 = .258$**						
	Moderate depression *N* = 59 *M (SD)*	Severe depression *N* = 41 *M (SD)*	*F* *p* ηp²					Pairwise	*p*
			DHA	S	I	G	IQ		
T1 score									
Low DHA	6.65 (1.61)	6.40 (2.07)	1.570	0.057	0.115	0.073	**7.401**	NS	NS
Moderate DHA	7.25 (1.68)	7.00 (1.41)	.214	.812	.892	.788	**.008***		
High DHA	6.94 (1.61)	6.78 (1.90)	.033	.001	.002	.001	**.074**		
T2 score									
Low DHA	9.87 (2.97)	8.91 (0.69)	1.733	0.923	0.323	0.000	**14.652**	NS	NS
Moderate DHA	10.85 (2.87)	9.10 (2.13)	.182	.339	.725	.982	**< .001***		
High DHA	10.25 (1.18)	10.28 (2.63)	.036	.010	.007	.000	**.137**		
T3 score									
Low DHA	11.09 (2.17)	11.50 (2.72)	1.096	0.184	0.641	3.039	**15.105**	NS	NS
Moderate DHA	11.70 (2.06)	10.38 (2.06)	.338	.669	.529	.085	**< .001***		
High DHA	11.75 (2.05)	11.94 (1.86)	.023	.002	.014	.032	**.141**		

Table 11 continued									
T4 score									
Low DHA	11.96 (2.35)	12.20 (2.20)	1.769	0.100	0.913	2.062	**31.252**	NS	NS
Moderate DHA	13.15 (1.73)	11.54 (3.05)	.176	.752	.405	.154	**< .001***		
High DHA	12.63 (1.09)	13.06 (1.51)	.037	.001	.019	.022	**.254**		
T5 score									
Low DHA	12.09 (2.28)	13.10 (1.60)	0.038	0.366	1.816	0.881	**19.510**	NS	NS
Moderate DHA	13.05 (1.79)	11.77 (1.88)	.963	.547	.169	.350	**< .001***		
High DHA	12.44 (1.63)	12.89 (1.64)	.001	.004	.038	.009	**.175**		
VLMT interference parameters	DHA: $F(6,182) = 0.933$, $p = .472$, $\eta_p^2 = .039$ S: $F(3,90) = 0.716$, $p = .545$, $\eta_p^2 = .023$ **I: $F(6,182) = 2.219$, $p = .052°$, $\eta_p^2 = .066$** G: $F(3,90) = 0.480$, $p = .697$, $\eta_p^2 = .016$ **IQ: $F(3,90) = 8.593$, $p = < .001***$, $\eta_p^2 = .223$**								
I									
Low DHA	7.13 (2.70)	5.90 (2.38)	0.066	0.804	0.753	1.131	**16.398**	NS	NS
Moderate DHA	6.60 (1.76)	5.92 (2.63)	.936	.372	.474	.290	**< .001***		
High DHA	6.25 (2.46)	6.39 (1.91)	001	.009	.016	.012	**.151**		
T6									
Low DHA	11.43 (2.76)	12.70 (2.36)	1.405	0.006	**4.337**	0.445	**12.435**	I: s/h > s/m	$p = .036$*
Moderate DHA	12.45 (2.21)	10.00 (2.35)	.251	.936	**.016***	.506	**.001***	I: m/m > s/m	$p = .021$*
High DHA	12.06 (1.95)	12.61 (1.29)	.030	.000	**.086**	.005	**.119**		
T5-6									
Low DHA	0.65 (1.56)	0.40 (1.58)	2.621	0.613	1.959	0.017	0.006	NS	NS
Moderate DHA	0.60 (1.60)	1.77 (1.64)	.078	.436	.147	.897	.936		
High DHA	0.38 (1.41)	0.28 (1.32)	.054	.007	.041	.000	.000		

Table 11
continued

VLMT Long-term memory parameters	DHA: $F(4,184) = 0.599$, $p = .664$, $\eta_p^2 = .013$ S: $F(2,91) = 0.181$, $p = .835$, $\eta_p^2 = .004$ I: $F(4,184) = 1.805$, $p = .130$, $\eta_p^2 = .038$ G: $F(2,91) = 0.488$, $p = .615$, $\eta_p^2 = .011$ **IQ: $F(2,91) = 11.721$, $p < .001$***, $\eta_p^2 = .205$**								
T7									
Low DHA	11.70 (2.79)	11.90 (2.51)	0.804	0.151	1.598	0.744	**19.794**	NS	NS
Moderate DHA	12.25 (2.95)	10.62 (2.18)	.450	.698	.208	.391	**< .001***		
High DHA	11.69 (2.02)	13.00 (1.33)	.017	.002	.034	.008	**0.117**		
T5-7									
Low DHA	0.39 (1.64)	1.20 (1.75)	1.110	0.011	1.860	0.031	1.802	NS	NS
Moderate DHA	0.80 (2.12)	1.15 (1.46)	.334	.916	.161	.860	.183		
High DHA	0.75 (1.44)	-0.11 (1.41)	.024	.000	.039	.000	.019		
Digits forward									
Low DHA	9.09 (2.18)	9.90 (1.37)	**3.342**	0.956	1.523	0.230	**25.145**	NS	NS
Moderate DHA	8.45 (1.50)	7.85 (1.41)	**.040***	.543	.224	.633	**< .001***		
High DHA	8.69 (1.66)	8.28 (2.08)	**.068**	.004	.032	.003	**.216**		
Digits backwards									
Low DHA	8.64 (2.36)	8.60 (1.17)	0.780	0.005	0.192	0.058	**17.851**	NS	NS
Moderate DHA	8.15 (1.81)	7.62 (1.26)	.461	.942	.826	.810	**< .001***		
High DHA	8.19 (1.64)	7.89 (1.61)	.017	.000	.004	.001	**.164**		

Note: GIX, global intelligence index. η_p^2= .01 (small), .06 (medium), .14 (large). l, low DHA status; m, moderate DHA status; h, high DHA status; m/l, moderately depressed with a low DHA status; m/m, moderately depressed with a moderate DHA status; m/h moderately depressed with a high DHA status; s/l, severely depressed with a low DHA status; s/m = severely depressed with a moderate DHA status; s/h = severely depressed with a high DHA status. Group sizes (*n*): m/l = 23; m/m = 20; m/h = 16; s/l n=10; s/m = 13; s/h = 18. Multivariate effects, pairwise comparisons: °borderline significant *$p < 0.05$, ***$p < .001$. Between-subjects effects: °borderline significant, *$p < .010$ (short-term memory), *$p < .017$ (interference), *$p < .025$ (long-term memory) after Bonferroni correction of significance level. Significant effects are marked in bold. T1-7, trials 1-7; NS, not significant.

3.4 Discussion

The current study investigated RBC EPA and DHA levels, as well as depression severity in relation to memory performance in a sample of 107 moderately to severely depressed youths. Contrary to previous findings that reported inverse associations between oily fish intake and depression severity (Bountziouka et al., 2009), in our sample severely depressed patients had significantly higher DHA and total omega-3 statuses compared to moderately depressed patients. Whereas negative associations between EPA status and depression severity have been reported (Adams et al., 1996), we found no significant differences concerning EPA status between moderately and depressed patients.

In our study, we examined potential cognitive deficits in depressed children and adolescents which have been inconsistently found in previous studies (Brooks et al., 2010; Goodall et al., 2018; Günther et al., 2004; Vilgis et al., 2015; Wagner et al., 2014) in contrast to research conducted in adult patient groups, where deficits seem more consistent (Ahern & Semkovska, 2017; R. S. C. Lee et al., 2012; Lim et al., 2013; Porter et al., 2015; Rock et al., 2014; Snyder, 2013; Wagner et al., 2012). Although most patients achieved average normative scores for both the VLMT and the digit span test, over 20% of the patients (compared to an expected 15.9% in a healthy population) achieved below average normative scores. These results indicate a tendency towards impaired verbal memory in depressed youths.

We further aimed at investigating potential negative associations between depression severity and cognitive functioning in depressed youths that so far have mostly been reported in adult patient groups (McClintock, Husain, Greer, & Cullum, 2010; McDermott & Ebmeier, 2009), with similar tendencies from research conducted in children and adolescents (Maalouf et al., 2011). Contrary to our hypothesis, in our sample we did not find any significant differences in verbal memory performance between moderately and severely depressed patients. Hence, we could not confirm any negative associations between depression severity and cognitive functions previously reported in adult patient groups (McClintock et al., 2010; McDermott & Ebmeier, 2009).

Most importantly, we were interested in memory performance in relation to EPA and DHA status, because mostly EPA supplementation has been associated with beneficial cognitive effects in youths (Chang et al., 2019; Emery et al., 2020), and beneficial cognitive effects would prove especially important in this vulnerable population. Our results indicated that patients with a high EPA status had steeper learning curves across the short-term memory trials of a verbal list learning test, compared to patients with a moderate or low EPA status. Compared to patients with a moderate or low EPA status, those with a high EPA status, seemed to remember more words faster, although they achieved equal scores in the first trial and again in the last two trials. This finding only partly confirmed our hypothesis that patients with a high EPA status would outperform patients with a low EPA status in verbal memory tests, because differences were only observed for the second and third trials and not overall. Moreover, these differences were only found for short-term memory parameters, whereas no significant effect for EPA status presented for any other VLMT parameter or the digit span test. However, we were able to confirm our hypothesis concerning DHA by finding no significant effect of DHA on any verbal memory parameter. Both results are in line with previous findings from meta-analyses on supplementation effects of EPA and DHA that suggested beneficial effects of EPA but not DHA on cognitive functioning (Chang et al., 2019; Emery et al., 2020) and effects in clinical rather than healthy populations (Emery et al., 2020). In contrast to our hypothesis, we were not able to confirm any superior effects of a high EPA status in severely compared to moderately depressed patients.

A number of limitations should be kept in mind when interpreting the reported results. First, no healthy control group was investigated; hence, no comparison between depressed and healthy children and adolescents could be made. Nevertheless, our data suggested that a somewhat larger proportion of participants than expected in a healthy population achieved below average normative scores in both tests. Importantly, the current study was based on a cross-sectional design. It is hence limited by the impossibility to draw conclusions about any causal relationships. Another methodological limitation lies in the small and unequally sized

subgroups formed by the two factors of depression severity and DHA and EPA status. Moreover, for several analyses the Levene's tests proved significant. However, rather conservative statistical methods for correction were applied throughout the analyses, minimizing the probability of a type-I error.

Our results further contribute to previous findings that reported some impairment considering cognitive functions (Vilgis et al., 2015) and especially memory performance (Günther et al., 2004) in depressed youths. Future studies should investigate differences between healthy and depressed individuals concerning memory performance in order to be able to further confirm these findings and make recommendations for cognitive assessments in this population. Surprisingly, the analyses of our sample revealed higher DHA and total omega-3 status in severely compared to moderately depressed patients. One explanation for this finding might lie in altered nutritional patterns in severely compared to moderately depressed youths. Moreover, considering the population investigated, low n-3 PUFA levels were expected to begin with, and hence, small ranges were presented. Wider ranges might therefore have produced different results. This explanation is, of course, only speculative. Although the reported analyses with EPA and DHA only contributed associations between RBC levels and verbal memory rather than effects of supplementation, they further corroborate evidence from meta-analyses that confirmed the beneficial supplementation effects of EPA but not DHA. Thus, our findings suggest that an increased dietary intake of EPA might prove beneficial for cognitive improvement or even remission in depressed youths. Based on our findings, future RCTs should investigate the effects of EPA compared to DHA supplementation in depressed children and adolescents to potentially establish a recommendation for a natural and easily accessible intervention for cognitive improvement or remission in depressed youths. Neuroimaging studies have tried to explain differences in supplementation effectivity between DHA and EPA. Bauer and colleagues (2014), for example, reported a reduction in functional activation in the left anterior cingulate cortex and shorter reaction times in the Stroop color-word task, following EPA rather than DHA supplementation, which, they argued, might rep-

resent stronger neural efficiency in EPA-supplemented compared to DHA-supplemented individuals. Biologically, however, the supplementation advantages of EPA over DHA have yet to be explained, considering EPA is found in much smaller concentrations within the brain compared to DHA (Bazinet & Layé, 2014; Weiser et al., 2016). As there is also a lack of understanding about the actual absorption and utilization of both EPA and DHA, it would be paramount to investigate the moderating effects of, for example, the microbiome, as differences might be expected, and these again might explain differential effects in different population

4 General Discussion

The general discussion of the present dissertation starts with the summary and integration of the most important findings. In a next step, strengths and limitations of the conducted studies are discussed, and implications and future directions are delineated. The dissertation ends with some concluding thoughts.

4.1 Summary and integration of findings

In this thesis, the role of n-3 PUFAs concerning cognitive test performance in children and adolescents was investigated using two independent scientific studies.

While some maternal supplementation studies have shown promising results concerning benefits of maternal n-3 PUFA supplementation on child growth and development during pregnancy, meta-analytic results are still equivocal (Gould et al., 2013; Lehner et al., 2020; Middleton et al., 2019). Most robust evidence exists for beneficial effects on visual acuity (European Food Safety Authority, 2009). Because brain development continues until the age of about 25, youths constitute a vulnerable subgroup for adverse effects of n-3 PUFA deficiency and cognitive complaints could have detrimental effects on educational attainment in youths. Due to the developmental course of the brain, the young brain might, however, simultaneously be most susceptible to protective effects and change, which in turn makes potential beneficial effects of n-3 PUFAs most probable in this population. Meta-analyses to date have, however, reported heterogeneous results (Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015; Jiao et al., 2014). The first study aimed at systematically reviewing previous findings concerning n-3 PUFA supplementation in youths reported by previous studies, tackling both heterogeneities as well as methodological and conceptual deficits of previous meta-analyses, which will be discussed in depth in the next chapter. The meta-analysis on the effects of n-3 PUFA supplementation on cognitive test performance in youths revealed several important findings. In this study, it was established that overall, there seems to be little evidence for a general beneficial effect of n-3 PUFA supplementation on cognitive test performance in youths. These results confirm the findings previously reported by Cooper and colleagues (2015). Some disagreement arises in comparison with the findings reported by Jiao and colleagues (2014) who found significant supplementation effects in infants concerning the mental development index (MDI). These differences could at least partially be explained by the lower number of

studies included in their MDI analysis, together with the fact that three of the included results were based on results reported by the same study. Small beneficial effects of EPA but not DHA were revealed in our meta-analysis. As no other meta-analysis so far has investigated efficacy differences between EPA and DHA, this constitutes a novel and important finding. The results, however, go in line with some preliminary findings for example reported by Bloch and Qawasmi (2011) where EPA dosage was positively associated with increased efficacy in treating ADHD symptoms and Cooper and colleagues (2015) who found that small treatment effects emerged for working memory in studies that supplemented with an adequate amount of EPA. In our study, tendencies towards effects in clinical rather than healthy populations were revealed, which confirms some previous findings where patients with ADHD seemed to benefit from supplementation (Bloch & Qawasmi, 2011; Chang et al., 2018). These findings are of great importance considering the debilitating effects of cognitive deficits, especially in young clinical populations (Fletcher, 2008; Morey-Nase et al., 2019). Altogether, there seemed to be no clear evidence for a specific domain that would benefit most from supplementation. Dosage was unrelated to study effect size which again confirms results from some previous meta-analyses (Chang et al., 2018; Cooper et al., 2015; Jiao et al., 2014) while contradicting others (Bloch & Qawasmi, 2011).

In adults, meta-analyses have reported promising results concerning effects of n-3 PUFA supplementation on depression symptomatology, hinting at potentially stronger effects of EPA rather than DHA (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019; Martins, 2009; Mocking et al., 2016). In children, this has yet not been confirmed (Zhang et al., 2019). Also, studies on cognitive effects within depressed subgroups are scarce (Knochel et al., 2015). Although previously reported results in depressed (Rogers et al., 2008), recovered (Niki Antypa et al., 2012) and adults “at risk” (Duffy et al., 2015) have provided little evidence for an association between n-3 PUFAs and cognitive functioning in depression, in youths, Vesco, Young, Arnold, and Fristad (2018) revealed decreased parent-rated impairments in executive functioning after a 12-weeks supplementation with n-3 PUFAs. Also, the results reported by Borsini and colleagues (2020), where EPA and DHA were associated with the prevention of glucocorticoid-induced reduction in human hippocampal neurogenesis, strongly suggest that n-3 PUFAs might be associated with cognitive outcomes in depression. No studies to date have investigated associations between n-3 PUFAs and verbal memory performance in depressed youths. The goal of the second study was to investigate potential associations between n-3 PUFA status, especially DHA and EPA status, and cognitive test performance in depressed youths, potentially paving the way for further investigation into a natural and easily accessible

treatment option for cognitive remission in this specific population. Based on findings from study 1 and previous studies that reported beneficial effects of especially EPA compared to DHA on both depression symptomatology (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019) as well as general cognitive test performance (Chang et al., 2019), study 2 investigated potential differences in association between EPA versus DHA status and cognitive test performance in depressed youths. Based on previously discussed methodological concerns about using subjective rating scales, high quality cognitive outcome assessment measures were used. Furthermore, domain-specific cognitive assessments were used for the evaluation of verbal memory performance only.

In our study sample, only minor cognitive deficits presented, which confirms previous findings that youths might be less severely affected by cognitive deficits (Goodall et al., 2018; Maalouf et al., 2011; Vilgis et al., 2015; Wagner et al., 2014) compared to adults (Knight & Baune, 2018; R. S. C. Lee et al., 2012; Marazziti et al., 2010; Rock et al., 2014). Findings further indicated that EPA status was positively associated with verbal memory performance, whereas DHA status was not. Depressed youths with a high EPA status had steeper learning curves concerning short-term memory parameters of a verbal learning task compared to those with a moderate or a low EPA status. These results both confirm our findings from study 1 as well as results reported for depression symptomatology in general (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019) and results reported for cognitive test performance in youths with ADHD (Chang et al., 2019). These results, supporting a potential positive association between EPA and verbal memory performance in youths, form a crucial basis for further investigation into potential beneficial supplementation effects in this vulnerable population. Preventing or diminishing cognitive complaints would prove most relevant because these cognitive deficits have been shown to persist even in the remitted stage (Biringer et al., 2007; Bo Jacob Hasselbalch et al., 2011; Semkovska et al., 2019), which would further prolong their debilitating effects. Contrary to studies in depressed adults that had shown negative associations between depression severity and cognitive test performance (McDermott & Ebmeier, 2009) and where severity had also proven a moderating factor in the association between n-3 PUFA supplementation efficacy in the treatment of depression symptoms (Appleton et al., 2010), in the population investigated, depression severity was unrelated to verbal memory performance.

Taken together, our results support a positive association between EPA but not DHA status as well as supplementation and cognitive test performance in children, with tendencies towards

stronger associations in clinical rather than healthy population. A specific association between EPA status and verbal memory performance in depressed youths was established.

4.2 Strengths and limitations of the conducted research

Both studies were based on previous research and have conceptual as well as methodological strengths that should be pointed out. However, although especially study 1 was conceptualized in order to address pitfalls of previous meta-analyses, a number of limitations also need to be considered when interpreting the study results.

4.2.1 Strengths

The meta-analysis conducted was conceptualized and prepared based on limitations from previous meta-analyses. Those limitations were successfully tackled by the following key factors. Meta-analyses have reported age-specific results using an artificial (e.g. legally defined) cut-off of, for example, 18 years of age for adulthood (Cooper et al., 2015). Instead, in our meta-analysis, we used a cut-off based on the developmental course of the brain. The lack of thorough and hence sometimes inaccurate classification of cognitive tests used within cognitive domains (Jiao et al., 2014) constitutes a further pitfall of previous meta-analyses which we tackled by thoroughly screening cognitive assessment measures within the included studies. Albeit providing no support for differential efficacy between certain cognitive domain, reporting domain- specific effects constituted a further strength. The separation rendered the results interpretable and avoided random selection of outcomes from each included study. Also, it accounted for potentially select effects of underlying neuroanatomical- and functional circuits involved in those cognitive functions. Vast differences in study formulations concerning n-3 PUFA dosage exist, which we analyzed using correlations between dosage and effect size. Results from studies using formulations with both n-3 and n-6 PUFAs have previously been pooled within one analysis (Bloch & Qawasmi, 2011; Chang et al., 2018; Cooper et al., 2015), which we prevented by excluding all studies with n-6 PUFAs in their study formulations. This constituted a very conservative but at the same time crucial measure in order to selectively assess n-3 PUFA supplementation effects. We were hence able to pinpoint effects attributable to only n-3 PUFAs with no bias from n-6 PUFAs. Many previous studies have not reported any comparisons between effects in healthy and clinical populations (Bloch & Qawasmi, 2011; Chang et al., 2018; Jiao et al., 2014). In our study, however, we performed subgroup analyses

based on clinical and healthy population subgroups which further allowed for differentiation of supplementation effects. Often, meta-analyses have not investigated efficacy differences between EPA and DHA supplementation (Chang et al., 2018; Jiao et al., 2014) although concentration differences within the brain are vast (Bazinet & Layé, 2014; McNamara & Carlson, 2006; Weiser et al., 2016). In our meta-analysis, subgroup analyses were run for subgroups with EPA-rich versus DHA-rich study formulations. Implementing these subgroup analyses enabled us to highlight their differential potential in relation to cognitive functioning. Heterogeneities also exist concerning the cognitive measures used, as some studies have reported results based on subjective rating scales (Abdullah et al., 2019; Bloch & Qawasmi, 2011) as opposed to objective measures of cognitive test performance (Chang et al., 2018; Cooper et al., 2015; Jiao et al., 2014). In our study, only studies reporting results on cognitive test performance were included, due to bias concerns discussed in the introductory section. As has been established in previous chapters, subjective and objective cognitive outcomes represent different entities and should hence not be mixed within a single meta-analysis. A further strength lies in the actual nature of this study, as with this meta-analysis a broad body of literature was systematically reviewed with a comprehensive and replicable search strategy. Also, all studies selected for analysis were RCTs and methodological quality was thoroughly assessed. Another important methodological success was reached by using change scores of cognitive test performance instead of only post-treatment scores in order to eliminate any pre-existing group differences. Lastly, potential effects of treatment duration and year of publication were successfully eliminated by confirming no association between these factors and the effect sizes reported of the respective studies. The goal of the meta-analysis was to reach a more specific conclusion about potential beneficial effects of n-3 PUFA supplementation on cognitive test performance in youths while especially targeting potential efficacy differences between EPA and DHA and effects in clinical versus healthy populations. At the time of analysis, there had yet been no meta-analysis investigating the separate and domain-specific effects of EPA and DHA supplementation on cognitive test performance in both clinical and healthy youths.

For the second study, further pivotal strengths should be highlighted. One of the major strengths constitutes the objective and validated measurement of verbal memory performance. Using the VLMT (Helmstaedter & Durwen, 1990) and the digit span test (Wechsler, 2003) enabled us to report results for cognitive test performance that were objectively measured with a validated test and could be interpreted using normative data. The same applies to the measurement of blood n-3 PUFA status. Instead of using subjective nutritional measures like for example dietary questionnaires which have proven largely unreliable (Harris & Klurfeld,

2011), an objective, standardized and widely accepted measure for n-3 PUFA blood status was used (Harris et al., 2013). Following the recommendation established in study 1, n-3 PUFA status was not investigated as a whole. EPA and DHA status associations with verbal memory performance were separately assessed, allowing for differentiation between these two types of n-3 PUFAs. Most importantly, this study was conducted in order to begin to fill a large research deficit in the field of both n-3 PUFAs and depression in youths but also n-3 PUFAs and cognition in depression. To our knowledge, this was the first study ever conducted investigating n-3 PUFA status in relation to cognitive test performance in depressed youths. General methodological strengths lie in the use of a substantial sample of depressed children and adolescents. Furthermore, diagnosis of MDD was assessed using standardized clinical interviews. As a whole, the sample was recruited and assessed as part of an RCT based on a high-quality design supported by the Swiss National Science Foundation.

4.2.2 Limitations

Although many strengths were highlighted in the previous section, a number of limitations of the conducted studies should also be addressed.

For the meta-analysis, the exclusion of seven studies due to missing data constitutes a serious drawback. Despite the effort of contacting the corresponding authors of these studies, only some of the missing data could be obtained, hence resulting in the exclusion of these studies. Although the exclusion of studies also supplementing n-6 PUFAs in their study formulations represents a crucial measure in order to be able to isolate n-3 PUFA effects, this led to the exclusion of a total of 25 studies, which greatly limited the statistical power of the reported results. Moreover, some of the excluded studies only supplemented a very small amount of n-6 PUFAs, but because there is no clear evidence suggesting a minimum dosage for any bodily effects, those studies were nevertheless excluded. While questionnaire outcomes were excluded based on the important notion that subjective and objective measure of cognitive functions should not be mixed within a single analysis, the results are limited to cognitive test performance, while effects on subjective cognitive functioning would be equally probable and interesting to assess. The results reported in our meta-analyses are hence also only marginally comparable with studies using self-rating questionnaires as study outcomes, for example in ADHD (Abdullah et al., 2019; Bloch & Qawasmi, 2011) and pediatric mood disorders (Vesco et al., 2018). Furthermore, effects on subjective cognitive complaints might even prove more relevant as these tend to be highly related to factors like education performance (Baars et al.,

2015). One of the most important drawbacks lies in the vast protocol heterogeneity of the included RCTs. This heterogeneity was mostly attributable to differences in n-3 PUFA dosage, intervention duration, cognitive tests and age of participants, reducing comparability of these studies. However, using random effects model, we were statistically able to reduce bias attributable to study heterogeneity. Even though we performed subgroup analyses for clinical and healthy study populations, especially the clinical subgroup population seamed very heterogeneous. Because of the limited number of studies within the subgroups of the clinical group, like ADHD, very low birth weight infants, malnourished and marginally nourished youths, youths with poor iron status, no separate analyses for all those groups could be run. This pitfall could only have been addressed if more studies could have been included in the meta-analysis, although the study heterogeneity problem was somewhat corrected for using a random-effects model. However, no separate conclusions about effects within the specific subgroups could be made. In general, the number of studies included in the analyses (and especially subgroup analyses) was very low, which made results statistically very sensitive to the addition of further data. Two studies were identified that seemed to have had great impact on heterogeneity and the associated effects sizes reported. We were however able to resolve this bias by successfully performing a sensitivity analysis. The removal of these studies did not impact the results and hence the conclusion of the meta-analysis. An additional drawback associated to the subgroup analyses was that EPA and DHA group formation was only based on the criterion of whether study formulations contained more EPA or more DHA. Hence, in most studies, the influence of the other type of n-3 PUFA could not be excluded. This limitation corresponds to a similar issue found in the meta-analysis by Cooper and colleagues (2015) who reported small treatment effects in studies which supplemented adequate EPA, however without any reference to the amount of DHA supplemented. Bloch and Qawasmi (2011) equally reported a positive association between higher doses of EPA and efficacy in treating ADHD symptoms, without being able to exclude effects of simultaneous DHA supplementation. Another pitfall lies in the outcome measure heterogeneity. Despite the categorization of outcome measures and the separation of results into different cognitive domains, scales used within one analysis differed greatly. Even though we thoroughly screened all cognitive assessment scales and placed them within cognitive domains, an issue extensively discussed in the introductory section still constituted a major limitation. This issue concerns the distinctions between the assessment of different cognitive domains, as definitions often overlap, and cognitive tasks often engage several cognitive domains simultaneously. Nevertheless, we were at least partially able to tackle this issue using standardized mean difference as an outcome measure. Our risk of bias analysis further revealed

several methodological flaws of included studies which might have substantially influenced study results. Only four studies were rated *low* across all bias risks (Cornu et al., 2018; McNamara et al., 2010; Richardson et al., 2012; Van Der Merwe et al., 2013) and "incomplete outcome data" and "blinding of participants and personnel" were the criteria most frequently rated *high*. These criteria are essential markers of study and design quality, hence high bias ratings strongly affect conclusions that can be drawn following the reported results. Lastly, many putative moderating or confounding variables such as pre- and posttreatment n-3 PUFA blood plasma concentrations could not be considered.

The most obvious limitation of the second study lies in its cross-sectional design. Because the omega-3 pMDD trial is still ongoing, consequently only baseline data could be analyzed for the second study. Hence, study 2 was limited by the impossibility to draw conclusions about causal relationships. Although n-3 PUFA status associations with cognitive test performance hint at potential supplementation effects, clear evidence can only be obtained using RCTs. This study hence only provides associative evidence for a relationship between n-3 PUFAs and verbal memory performance in youths. Another major drawback lies in the absence of a healthy control group. Not being able to compare the findings in depressed youths with findings in healthy children and adolescents largely diminished the generalizability of our study results. Therefore, we were not able to draw any conclusions about the general level of RBC n-3 PUFAs or cognitive performance in this study population. Another quite general limitation lies in the limited study sample. Although cognitive data would have been available for over 180 patients, only 107 blood samples had been analyzed at time of analysis, limiting the statistical robustness of the reported results. While the objective tasks used for verbal memory performance constitutes a strength of the study, it also limits the reported results to cognitive test performance. Memory complaints subjectively perceived in everyday life were not included in the analysis, whereas these potentially represent a more relevant outcome associated with an individual's everyday functioning. As problems concentrating constitute a main diagnostic criterion for pMDD (American Psychiatric Association, 2013), potentially evaluating these using self-report questionnaires would prove more accurate for the purpose of describing the cognitive deficits associated with pMDD. This might be associated with an issue discussed in the introductory section, where cognitive complaints might not be adequately captured in objective and hence artificial testing situations. This assumption has so far been supported by findings in depressed youths who reported cognitive deficits (Morey-Nase et al., 2019), whereas results on reduced cognitive performance are heterogeneous (Goodall et al., 2018; Maalouf et al.,

2011; Vilgis et al., 2015; Wagner et al., 2014). Whether subjective or objective cognitive impairments are more predictive of impaired everyday functioning is, however, still unclear (Naismith et al., 2007; Potvin et al., 2016). Furthermore, the issue of bias through negative self-perception would also have to be considered (Lahr et al., 2007). Although many confounding differences between the n-3 PUFA and severity groups were checked for (e.g. IQ and duration of depression), bias through potentially unidentified group differences cannot be fully excluded. Lastly, because significant group differences were only found for short-term memory verbal list learning parameters and no other memory parameter, only very limited evidence for any relationship between EPA status and verbal memory performance was given. Although the learning curves in those with high EPA status were steeper, there were no differences concerning the number of words remembered in the last trial. This hence poses some questions concerning any relevance in everyday life and functioning.

4.3 Important contributions

The results reported in the two studies conducted as part of this dissertation suggest some pivotal implications which will be discussed in the following chapter. Future directions are proposed in the second part of this section.

4.3.1 Potential implications

Considering the results reported in study 1 and the limitations discussed, we can make no clear recommendations for n-3 PUFA supplementation in youths in order to improve cognitive test performance. However, the small effects found for EPA-rich formulations and the tendency towards stronger effects in clinical compared to healthy populations, suggests that EPA-rich formulations might prove useful as supportive measures in holistic treatments of cognitive complaints in vulnerable or clinical populations. This potential implication was also supported by the results from study 2, where EPA status was associated with verbal memory performance in a young depressed population with minor deficits concerning verbal memory. Positive cognitive effects of n-3 PUFA supplementation, especially in depressed youths could prove essential, as treatment with antidepressant medication has proven heterogeneously effective (Bennabi et al., 2019; Biringer et al., 2009; Bortolato et al., 2016; Prado et al., 2018; Rosenblat et al., 2015; Shilyansky et al., 2016; Skandali et al., 2018; Zuckerman et al., 2018). Also, antidepressants are associated with a wide range of side effects like for example sexual dysfunction

(Carvalho et al., 2016; Outhoff, 2010), nausea (Carvalho et al., 2016), weight changes (Carvalho et al., 2016; Serretti & Porcelli, 2018), sleep disruption (Aszalós, 2006; Carvalho et al., 2016) and even increased suicidality, especially in younger individuals (Brent, 2016; Sharma et al., 2016). In Switzerland, no antidepressant medication has yet been approved for the treatment of depressive symptoms in youths, necessitating off-label prescriptions. These issues further emphasize the need for alternatives. Should future research succeed in disentangling the previously discussed effects of potential moderating factors and come to a more definite conclusion, this natural and easily accessible supplement could be used without concern about any major potential side effects.

Further potential implications arise from the results reported in study 2. The results indicate that depression severity might not be associated with verbal memory performance. These results go in line with isolated results in youths (Maalouf et al., 2011) and results reported in adult populations (McDermott & Ebmeier, 2009), where executive functions rather than semantic memory were associated with depression severity. Consequently, any associations found with subjective cognitive measures might either be attributable to the artificial testing environment of objective tests or might hint at a bias from negative self-perception (Lahr et al., 2007; Sachs-Ericsson et al., 2008). Although no healthy control group was included as a comparison for verbal memory performance, the results showed only slight impairments in this sample of depressed youths. As has been previously discussed, this might be explained by the shorter duration of the disease compared to adult patients, because cumulative duration of depressive episodes has been associated with diminished cognitive functioning (B. J. Hasselbalch et al., 2013) and smaller hippocampal grey matter (Arnone et al., 2013). This further highlights the importance of early intervention in depressed individuals. Because n-3 PUFA are vital for neurodevelopment (J. Baumgartner, 2016; Bazinet & Layé, 2014; Innis, 2008; Koletzko et al., 2008; Lauritzen et al., 2016; Sun et al., 2018) and potential neuroprotective effects of especially EPA related to grey matter atrophy of the hippocampal and parahippocampal area have been reported (Samieri et al., 2012), our results further contribute to the assumption that n-3 PUFAs might prove important in the prevention or reduction of cognitive complaints in depressed youths. When treated at an early stage, potential debilitating effects on cognitive functioning that might result from longer illness duration might be prevented and hence negative effects on long-term educational and personal attainment could potentially be reduced. The potential neuroprotective effects of n-3 PUFAs in depression were recently even further supported by the already previously mentioned findings reported by Borsini and colleagues (2020),

who were able to confirm that both DHA and EPA prevented glucocorticoid-induced reduction in human hippocampal neurogenesis and increase in apoptosis.

4.3.2 Future directions

A general recommendation that we were able to establish from both study 1 and 2 is that EPA and DHA effects should be investigated separately and that individual factors such as nutritional status and baseline cognitive functioning level should be considered. Most importantly, future research should investigate ideal supplementation doses of EPA and DHA and potentially ideal ratios of n-3 PUFAs and n-6 PUFAs, due to their competitive role within the membrane (Carrié et al., 2000; Neuringer et al., 1986; Simopoulos, 2008). A recently published meta-analysis by van der Wurff (2020) already established improved cognition in typically developing children when the omega-3 index rose to >6% and in studies with daily supplementation dose of ≥450 mg DHA + EPA. However, evidence for ideal n-3/n-6 PUFA ratios in relation to cognitive test performance in youths is still lacking. Also, because little is known about the actual absorption and utilization of n-3 PUFAs the impact of for example the individual microbiome should be investigated. This has to date mainly been done concerning the role of n-3 PUFAs and the microbiome in relation to neurodegenerative disorders (Hort et al., 2020). Many potential interactions with other substances and nutrients like for example antioxidant vitamins (Assmann et al., 2018) and B vitamins (Jernerén et al., 2019) were neither addressed in study 1 nor study 2 and could prove important. Most importantly, moderating factors like for example obesity, inflammatory status, pre- and post- blood levels of n-3 and n-6 PUFAs and interactions with gene variations like the ApoEε4 allele (where associations with cognitive decline have been reported (Samieri et al., 2011)) could prove important and should hence be considered in the evaluation of potential beneficial effects of supplementation. Identifying specific individual predictors of response together with the identification of specific subgroups that benefit most of n-3 PUFA supplementation would significantly specify and thereby improve recommendations for supplementation. Future studies should assess potential associations between n-3 PUFA status or supplementation and subjective cognitive functioning which was neither addressed in study 1 nor study 2. The artificial testing environment for objective cognitive testing could have masked potential beneficial effects on cognitive functioning in everyday life, better captured and evaluated through subjective outcome measures. Because especially studies on ADHD (Bloch & Qawasmi, 2011) but also studies in depressed

youths (Vesco et al., 2018) have reported beneficial cognitive effects of n-3 PUFA supplementation assessed using self-rating questionnaire, investigating differential outcomes depending on the cognitive measure applied could prove valuable. The results reported in study 2 pave the way for future RCTs investigating the effects of n-3 PUFA supplementation on cognitive test performance in depressed youths. Our results contributed evidence towards an association between EPA status and verbal memory performance in depressed youths. As we were once again able to support the already previously discussed recommendation of separately assessing effects of EPA and DHA, future studies should now further investigate the relationship between EPA and DHA status and cognitive test performance in other cognitive domains. Although study 1 provided no evidence for a certain cognitive domain that would benefit the most from supplementation, results nevertheless suggested that effects might not be equal between domains.

4.4 Conclusion

Previous research has established the vital role of n-3 PUFAs in neurodevelopment (J. Baumgartner, 2016; J. Baumgartner et al., 2012; Bazinet & Layé, 2014; Koletzko et al., 2008) and suggested that n-3 PUFA supplementation during gestation might positively impact neurodevelopmental outcomes (Middleton et al., 2019). Consequently, research on potential cognitive effects of supplementation after birth have gained interest within several research fields. In youths, where brain development is still ongoing, and especially in depressed youths, where cognitive complaints constitute a main symptom (American Psychiatric Association, 2013), beneficial cognitive effects of n-3 PUFAs could prove essential. This should be especially emphasized considering the heterogeneous efficacy reported for antidepressant treatment (Bennabi et al., 2019; Biringer et al., 2009; Bortolato et al., 2016; Prado et al., 2018; Rosenblat et al., 2015; Shilyansky et al., 2016; Skandali et al., 2018; Zuckerman et al., 2018) and the associated severe side effects like for example increased suicidality especially in younger individuals (Brent, 2016; Sharma et al., 2016). Because, especially in depressed youths, cognitive complaints can have debilitating effects and negatively impact educational attainment and everyday functioning (Fletcher, 2008; Morey-Nase et al., 2019), preventing or reducing such complaints could prove essential.

The present dissertation dealt with the role of n-3 PUFAs in cognitive functioning in youths. With the use of a meta-analysis, previous findings on the effects of n-3 PUFA supplementation on cognitive test performance in youths was investigated, specifically tackling limitations of

previous meta-analyses. By cross-sectionally investigating associations between RBC DHA and EPA levels and verbal memory performance in a sample of depressed youths, the second study aimed at establishing potential associations between specific n-3 PUFAs and a specific cognitive domain. Taken together, our results suggest that EPA but not DHA might prove beneficial in the promotion of cognitive functioning in youths and that clinical rather than typically developing youths might benefit. These results could prove especially valuable in relation to pMDD, considering that not only cognitive effects of EPA supplementation but also effects on emotional symptoms might be expected (Grosso, Pajak, et al., 2014; Hallahan et al., 2016; Liao et al., 2019; Martins, 2009; Mocking et al., 2016). However, optimal dosage and potentially optimal ratios between n-3 and n-6 PUFAs are in need of further investigation. Also, little is known about exact mechanisms of action, especially in relation to EPA. Research on the role of moderating factors is also seriously lacking. The discussed results presented in this dissertation, however, support first evidence for the recommendation of EPA supplementation in clinical populations. With the findings reported and discussed in this thesis we have significantly advanced the understanding of the role of n-3 PUFAs related to cognitive functioning in youths. Future findings confirming a beneficial role of n-3 PUFAs on cognitive functioning in depressed children and adolescent could establish the recommendation of a natural treatment approach potentially tackling both emotional as well as cognitive symptoms of this debilitating disease.

References

Abdelhamid, A. S., Brown, T. J., Brainard, J. S., Biswas, P., Thorpe, G. C., Moore, H. J., … Hooper, L. (2018). Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews*, *2018*(7). https://doi.org/10.1002/14651858.CD003177.pub3

Abdullah, M., Jowett, B., Whittaker, P. J., & Patterson, L. (2019). The effectiveness of omega-3 supplementation in reducing ADHD associated symptoms in children as measured by the Conners' rating scales: A systematic review of randomized controlled trials. *Journal of Psychiatric Research*, *110*, 64–73. https://doi.org/10.1016/j.jpsychires.2018.12.002

Abercrombie, H. C., Jahn, A. L., Davidson, R. J., Kern, S., Kirschbaum, C., & Halverson, J. (2011). Cortisol's effects on hippocampal activation in depressed patients are related to alterations in memory formation. *Journal of Psychiatric Research*, *45*(1), 15–23. https://doi.org/10.1016/j.jpsychires.2010.10.005

Able, J. A., Liu, Y., Jandacek, R., Rider, T., Tso, P., & McNamara, R. K. (2014). Omega-3 fatty acid deficient male rats exhibit abnormal behavioral activation in the forced swim test following chronic fluoxetine treatment: Association with altered 5-HT1A and alpha2A adrenergic receptor expression. *Journal of Psychiatric Research*, *50*(1), 42–50. https://doi.org/10.1016/j.jpsychires.2013.11.008

Abubakari, A.-R., Naderali, M.-M., & Naderali, E. K. (2014). Omega-3 fatty acid supplementation and cognitive function: are smaller dosages more beneficial? *International Journal of General Medicine*, *7*, 463–473. https://doi.org/10.2147/IJGM.S67065

Adams, P. B., Lawson, S., Sanigorski, A., & Sinclair, A. J. (1996). Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids*, *31*(1), S157–S161. https://doi.org/10.1007/bf02637069

Ahern, E., & Semkovska, M. (2017). Cognitive functioning in the first-episode of major depressive disorder: A systematic review and meta-analysis. *Neuropsychology*, *31*(1), 52–72. https://doi.org/10.1037/neu0000319

Alice, M., Baptista, T., Santos, R. L., Kimura, N., Lacerda, I. B., Johannenssen, A., … Dourado, N. (2016). Quality of life in young onset dementia: an updated systematic review. *Trends in Psychiatry and Psychotherapy*, *38*(1), 6–13.

Almaas, A. N., Tamnes, C. K., Nakstad, B., Henriksen, C., Walhovd, K. B., Fjell, A. M., … Iversen, P. O. (2016). Long-chain polyunsaturated fatty acids and cognition in VLBW infants at 8 years: An RCT. *World Review of Nutrition and Dietetics*, *114*, 61. https://doi.org/10.1159/000441922

Althubaiti, A. (2016). Information bias in health research: Definition, pitfalls, and adjustment methods. *Journal of Multidisciplinary Healthcare*, *9*, 211–217. https://doi.org/10.2147/JMDH.S104807

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental*

Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (Vol. 1). Arlington, VA: American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890423349

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: 5th Edn. In *Diagnostic and statistical manual of mental disorders: 5th Edn*. Washington DC: American Psychiatric Publishing.

Amminger, G. P., Schäfer, M. R., Schlögelhofer, M., Klier, C. M., & McGorry, P. D. (2015). Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. *Nature Communications*, *6*(1), 7934. https://doi.org/10.1038/ncomms8934

Anderson, B. M., & Ma, D. W. L. (2009). Are all n-3 polyunsaturated fatty acids created equal? *Lipids in Health and Disease*, *8*. https://doi.org/10.1186/1476-511X-8-33

Angst, J., Paksarian, D., Cui, L., Merikangas, K. R., Hengartner, M. P., Ajdacic-Gross, V., & Rössler, W. (2016). The epidemiology of common mental disorders from age 20 to 50: Results from the prospective Zurich cohort Study. *Epidemiology and Psychiatric Sciences*, *25*(1), 24–32. https://doi.org/10.1017/S204579601500027X

Antypa, N, Van der Does, A., Smelt, A., & Rogers, R. (2009). Omega-3 fatty acids (fish-oil) and depression-related cognition in healthy volunteers. *Journal of Psychopharmacology*, *23*(7), 831–840. https://doi.org/10.1177/0269881108092120

Antypa, Niki, Smelt, A. H. M., Strengholt, A., & Van Der Does, A. J. W. (2012). Effects of omega-3 fatty acid supplementation on mood and emotional information processing in recovered depressed individuals. *Journal of Psychopharmacology*, *26*(5), 738–743. https://doi.org/10.1177/0269881111424928

Appleton, K. M., Rogers, P. J., & Ness, A. R. (2010). Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *American Journal of Clinical Nutrition*, *91*(3), 757–770. https://doi.org/10.3945/ajcn.2009.28313

Appleton, K. M., Woodside, J. V., Yarnell, J. W. G., Arveiler, D., Haas, B., Amouyel, P., … Evans, A. (2007). Depressed mood and dietary fish intake: Direct relationship or indirect relationship as a result of diet and lifestyle? *Journal of Affective Disorders*, *104*(1–3), 217–223. https://doi.org/10.1016/j.jad.2007.03.012

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., … Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment*, *9*, 449–461. https://doi.org/10.2147/NDT.S39776

Arnone, D., Mckie, S., Elliott, R., Juhasz, G., Thomas, E. J., Downey, D., … Anderson, I. M. (2013). State-dependent changes in hippocampal grey matter in depression. *Molecular Psychiatry*, *18*(12), 1265–1272. https://doi.org/10.1038/mp.2012.150

Assmann, K. E., Adjibade, M., Hercberg, S., Galan, P., & Kesse-Guyot, E. (2018). Unsaturated fatty acid intakes during midlife are positively associated with later cognitive function in older adults with modulating effects of antioxidant supplementation. *Journal of Nutrition*, *148*(12), 1938–1945. https://doi.org/10.1093/jn/nxy206

Aszalós, Z. (2006). Effects of antidepressants on sleep. *Orvosi Hetilap*, *147*(17), 773–783.

Ateş, C., Kaymaz, Ö., Kale, H. E., & Tekindal, M. A. (2019). Comparison of Test Statistics of Nonnormal and Unbalanced Samples for Multivariate Analysis of Variance in terms of Type-I Error Rates. *Computational and Mathematical Methods in Medicine*, *2019*. https://doi.org/10.1155/2019/2173638

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: Possible implications for functional neuropathology. *British Journal of Psychiatry*, *178*(MARCH.), 200–206. https://doi.org/10.1192/bjp.178.3.200

Avenevoli, S., Swendsen, J., He, J. P., Burstein, M., & Merikangas, K. R. (2015). Major Depression in the National Comorbidity Survey–Adolescent Supplement: Prevalence, Correlates, and Treatment. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(1), 37-44.e2. https://doi.org/10.1016/j.jaac.2014.10.010

Baars, M. A. E., Nije Bijvank, M., Tonnaer, G. H., & Jolles, J. (2015). Self-report measures of executive functioning are a determinant of academic performance in first-year students at a university of applied sciences. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01131

Babcoc, K. (1931). an Experiment in the Measurement of Mental Deterioration. *The Journal of Nervous and Mental Disease*, *74*(3), 375. https://doi.org/10.1097/00005053-193109000-00024

Bartl, J., Walitza, S., & Grünblatt, E. (2014). Enhancement of cell viability after treatment with polyunsaturated fatty acids. *Neuroscience Letters*, *559*, 56–60. https://doi.org/10.1016/j.neulet.2013.11.023

Bauer, I., Hughes, M., Rowsell, R., Cockerell, R., Pipingas, A., Crewther, S., & Crewther, D. (2014). Omega-3 supplementation improves cognition and modifies brain activation in young adults. *Human Psychopharmacology*, *29*(2), 133–144. https://doi.org/10.1002/hup.2379

Baumgartner, J. (2016). Effects of Omega-3 Fatty Acid Supplementation on Cognition in Children. In *Handbook of Lipids in Human Function* (pp. 331–375). Elsevier. https://doi.org/10.1016/B978-1-63067-036-8.00012-3

Baumgartner, J., Smuts, C. M., Malan, L., Kvalsvig, J., Van Stuijvenberg, M. E., Hurrell, R. F., & Zimmermann, M. B. (2012). Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition in school children: A randomized, double-blind, placebo-controlled intervention in South Africa. *American Journal of Clinical Nutrition*, *96*(6), 1327–1338. https://doi.org/10.3945/ajcn.112.041004

Baumgartner, N., Häberling, I., Emery, S., Strumberger, M., Nalani, K., Erb, S., … Berger, G. (2020). When parents and children disagree: Informant discrepancies in reports of depressive symptoms in clinical interviews. *Journal of Affective Disorders*, *272*, 223–230. https://doi.org/10.1016/j.jad.2020.04.008

Bazinet, R. P., & Layé, S. (2014). Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nature Reviews Neuroscience*, *15*(12), 771–785. https://doi.org/10.1038/nrn3820

Belge, J. B., Van Diermen, L., Sabbe, B., Parizel, P., Morrens, M., Coppens, V., … Van Eijndhoven, P. (2020). Inflammation, Hippocampal Volume, and Therapeutic Outcome following Electroconvulsive Therapy in Depressive Patients: A Pilot Study. *Neuropsychobiology*. https://doi.org/10.1159/000506133

Belujon, P., & Grace, A. A. (2017). Dopamine system dysregulation in major depressive disorders. *International Journal of Neuropsychopharmacology*, *20*(12), 1036–1046. https://doi.org/10.1093/ijnp/pyx056

Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *The Clinical Neuropsychologist*, *12*(1), 43–55. https://doi.org/10.1076/clin.12.1.43.1726

Bennabi, D., Haffen, E., & Van Waes, V. (2019). Vortioxetine for Cognitive Enhancement in Major Depression: From Animal Models to Clinical Research. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00771

Berger, M. E., Smesny, S., Kim, S. W., Davey, C. G., Rice, S., Sarnyai, Z., … Amminger, G. P. (2017). Omega-6 to omega-3 polyunsaturated fatty acid ratio and subsequent mood disorders in young people with at-risk mental states: a 7-year longitudinal study. *Translational Psychiatry*, *7*(8), e1220. https://doi.org/10.1038/tp.2017.190

Beydoun, M. A., Obhi, H. K., Weiss, J., Canas, J. A., Beydoun, H. A., Evans, M. K., & Zonderman, A. B. (2019). Systemic inflammation is associated with depressive symptoms differentially by sex and race: a longitudinal study of urban adults. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0408-2

Birch, E. E., Garfield, S., Castañeda, Y., Hughbanks-Wheaton, D., Uauy, R., & Hoffman, D. (2007). Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. *Early Human Development*, *83*(5), 279–284. https://doi.org/10.1016/j.earlhumdev.2006.11.003

Birch, E. E., Garfield, S., Hoffman, D. R., Uauy, R., & Birch, D. G. (2000). A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Developmental Medicine and Child Neurology*, *42*(3), 174–181. https://doi.org/10.1017/S0012162200000311

Bird, C. M., & Burgess, N. (2008). The hippocampus and memory: Insights from spatial processing. *Nature Reviews Neuroscience*, *9*(3), 182–194. https://doi.org/10.1038/nrn2335

Biringer, E., Mykletun, A., Sundet, K., Kroken, R., Stordal, K. I., & Lund, A. (2007). A longitudinal analysis of neurocognitive function in unipolar depression. *Journal of Clinical and Experimental Neuropsychology*, *29*(8), 879–891. https://doi.org/10.1080/13803390601147686

Biringer, E., Rongve, A., & Lund, A. (2009). A Review of Modern Antidepressants Effects on Neurocognitive Function. *Current Psychiatry Reviews*, *5*(3), 164–174. https://doi.org/10.2174/157340009788971137

Bloch, M. H., & Hannestad, J. (2012). Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Molecular Psychiatry*, *17*(12), 1272–1282. https://doi.org/10.1038/mp.2011.100

Bloch, M. H., & Qawasmi, A. (2011). Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: Systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(10), 991–1000. https://doi.org/10.1016/j.jaac.2011.06.008

Borsini, A., Stangl, D., Jeffries, A. R., Pariante, C. M., & Thuret, S. (2020). The role of omega-3 fatty acids in preventing glucocorticoid-induced reduction in human hippocampal neurogenesis and increase in apoptosis. *Translational Psychiatry*, *10*(1). https://doi.org/10.1038/s41398-020-00908-0

Bortolato, B., Miskowiak, K. W., Köhler, C. A., Maes, M., Fernandes, B. S., Berk, M., & Carvalho, A. F. (2016). Cognitive remission: A novel objective for the treatment of major depression? *BMC Medicine*, *14*(1). https://doi.org/10.1186/s12916-016-0560-3

Bos, D. J., Oranje, B., Veerhoek, E. S., Van Diepen, R. M., Weusten, J. M. H., Demmelmair, H., … Durston, S. (2015). Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder. *Neuropsychopharmacology*, *40*(10), 2298–2306. https://doi.org/10.1038/npp.2015.73

Boucher, O., Burden, M. J., Muckle, G., Saint-Amour, D., Ayotte, P., Dewailly, E., … Jacobson, J. L. (2011). Neurophysiologic and neurobehavioral evidence of beneficial effects of prenatal omega-3 fatty acid intake on memory function at school age. *The American Journal of Clinical Nutrition*, *93*(5), 1025–1037. https://doi.org/10.3945/ajcn.110.000323

Bountziouka, V., Polychronopoulos, E., Zeimbekis, A., Papavenetiou, E., Ladoukaki, E., Papairakleous, N., … Panagiotakos, D. (2009). Long-term fish intake is associated with less severe depressive symptoms among elderly men and women: The MEDIS (MEDiterranean ISlands Elderly) epidemiological study. *Journal of Aging and Health*, *21*(6), 864–880. https://doi.org/10.1177/0898264309340693

Bourre, J. M. (2004). Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing. *The Journal of Nutrition, Health and Aging*, *8*(1279-7707 (Print)), 163–174. https://doi.org/10.1088/1478-3975/10/1/016001

Boyle, M. P., Brewer, J. A., Funatsu, M., Wozniak, D. F., Tsien, J. Z., Izumi, Y., & Muglia, L. J. (2005). Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(2), 473–478. https://doi.org/10.1073/pnas.0406458102

Bradberry, J. C., & Hilleman, D. E. (2013). Overview of omega-3 fatty acid therapies. *P & T : A Peer-Reviewed Journal for Formulary Management*, *38*(11), 681–691. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24391388%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3875260

Brenna, J. T. (2002). Efficiency of conversion of α-linolenic acid to long chain n-3 fatty acids in man. *Current Opinion in Clinical Nutrition and Metabolic Care*, *5*(2), 127–132. https://doi.org/10.1097/00075197-200203000-00002

Brent, D. A. (2016). Antidepressants and Suicidality. *Psychiatric Clinics of North America*, *39*(3), 503–512. https://doi.org/10.1016/j.psc.2016.04.002

Breslau, J., Gilman, S. E., Stein, B. D., Ruder, T., Gmelin, T., & Miller, E. (2017). Sex differences in recent first-onset depression in an epidemiological sample of adolescents. *Translational Psychiatry*, *7*(5), e1139. https://doi.org/10.1038/tp.2017.105

Brew, B. K., Toelle, B. G., Webb, K. L., Almqvist, C., & Marks, G. B. (2015). Omega-3 supplementation during the first 5 years of life and later academic performance: A randomised controlled trial. *European Journal of Clinical Nutrition*, *69*(4), 419–424. https://doi.org/10.1038/ejcn.2014.155

Brooks, B. L., Iverson, G. L., Sherman, E. M. S., & Roberge, M. C. (2010). Identifying cognitive problems in children and adolescents with wepression using computerized neuropsychological testing. *Applied Neuropsychology*, *17*(1), 37–43. https://doi.org/10.1080/09084280903526083

Bruder, G. E., Alvarenga, J. E., Alschuler, D., Abraham, K., Keilp, J. G., Hellerstein, D. J., … McGrath, P. J. (2014). Neurocognitive predictors of antidepressant clinical response. *Journal of Affective Disorders*, *166*, 108–114. https://doi.org/10.1016/j.jad.2014.04.057

Buckley, M. T., Racimo, F., Allentoft, M. E., Jensen, M. K., Jonsson, A., Huang, H., … Nielsen, R. (2017). Selection in Europeans on fatty acid desaturases associated with dietary changes. *Molecular Biology and Evolution*, *34*(6), 1307–1318. https://doi.org/10.1093/molbev/msx103

Calderon, F., & Kim, H.-Y. (2004). Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *Journal of Neurochemistry*, *90*(6), 1540–1540. https://doi.org/10.1111/j.1471-4159.2004.02808.x

Cambridge, O. R., Knight, M. J., Mills, N., & Baune, B. T. (2018). The clinical relationship between cognitive impairment and psychosocial functioning in major depressive disorder: A systematic review. *Psychiatry Research*, *269*, 157–171. https://doi.org/10.1016/j.psychres.2018.08.033

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower Hippocampal Volume in Patients Suffering from depression: A Meta-Analysis. *American Journal of Psychiatry*, *161*(4), 598–607. https://doi.org/10.1176/appi.ajp.161.4.598

Canhada, S., Castro, K., Perry, I. S., & Luft, V. C. (2017). Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review. *Nutritional Neuroscience*, 1–10. https://doi.org/10.1080/1028415X.2017.1321813

Cao, D., Kevala, K., Kim, J., Moon, H. S., Jun, S. B., Lovinger, D., & Kim, H. Y. (2009). Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *Journal of Neurochemistry*, *111*(2), 510–521. https://doi.org/10.1111/j.1471-4159.2009.06335.x

Carlson, S. E., & Werkman, S. H. (1996). A randomized trial of visual attention of preterm infants fed docosahexaenoic acid until two months. *Lipids*, *31*(1), 85–90.

Carney, R. M., Steinmeyer, B. C., Freedland, K. E., Rubin, E. H., Rich, M. W., & Harris, W. S. (2016). Baseline blood levels of omega-3 and depression remission: A secondary analysis of data from a placebo-controlled trial of omega-3 supplements. *Journal of Clinical Psychiatry*, *77*(2), e138–e143. https://doi.org/10.4088/JCP.14m09660

Carrié, I., Clément, M., De Javel, D., Francès, H., & Bourre, J. M. (2000). Specific phospholipid fatty acid composition of brain regions in mice: Effects of n-3 polyunsaturated fatty acid deficiency and phospholipid supplementation. *Journal of Lipid Research*, *41*(3), 465–472. https://doi.org/10.1016/S0022-2275(20)34485-0

Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and Psychosomatics*, *85*(5), 270–288. https://doi.org/10.1159/000447034

Carver, J. D., Benford, V. J., Han, B., & Cantor, A. B. (2001). The relationship between age and the fatty acid composition of cerebral cortex and erythrocytes in human subjects. *Brain Research Bulletin*, *56*(2), 79–85. https://doi.org/10.1016/S0361-9230(01)00551-2

Castillo, P. E., Younts, T. J., Chávez, A. E., & Hashimotodani, Y. (2012). Endocannabinoid Signaling and Synaptic Function. *Neuron*, *76*(1), 70–81. https://doi.org/10.1016/j.neuron.2012.09.020

Chalon, S. (2006). Omega-3 fatty acids and monoamine neurotransmission. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *75*(4–5), 259–269. https://doi.org/10.1016/j.plefa.2006.07.005

Chang, J. P. C., Su, K. P., Mondelli, V., & Pariante, C. M. (2018). Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. *Neuropsychopharmacology*, *43*(3), 534–545. https://doi.org/10.1038/npp.2017.160

Chang, J. P. C., Su, K. P., Mondelli, V., Satyanarayanan, S. K., Yang, H. T., Chiang, Y. J., … Pariante, C. M. (2019). High-dose eicosapentaenoic acid (EPA) improves attention and vigilance in children and adolescents with attention deficit hyperactivity disorder (ADHD) and low endogenous EPA levels. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0633-0

Chao, M. V. (2003). Neurotrophins and their receptors: A convergence point for many signalling pathways. *Nature Reviews Neuroscience*, *4*(4), 299–309. https://doi.org/10.1038/nrn1078

Chen, W., Tofler, G., McEwen, B., Ward, C., & Morel-Kopp, M.-C. (2013). Effects of omega-3 polyunsaturated fatty acids on platelet function in healthy subjects and subjects with cardiovascular disease. *Seminars in Thrombosis and Hemostasis*, *39*(01), 025–032. https://doi.org/10.1055/s-0032-1333309

Clark, L., Chamberlain, S. R., & Sahakian, B. J. (2009). Neurocognitive Mechanisms in Depression: Implications for Treatment. *Annual Review of Neuroscience*, *32*(1), 57–74.

https://doi.org/10.1146/annurev.neuro.31.060407.125618

Clarke, J. T. R., Cullen-Dean, G., Regelink, E., Chan, L., & Rose, V. (1990). Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. *The Journal of Pediatrics*, *116*(1), 139–141. https://doi.org/10.1016/S0022-3476(05)81666-X

Clayton, E. H., Hanstock, T. L., Hirneth, S. J., Kable, C. J., Garg, M. L., & Hazell, P. L. (2009). Reduced mania and depression in juvenile bipolar disorder associated with long-chain ω-3 polyunsaturated fatty acid supplementation. *European Journal of Clinical Nutrition*, *63*(8), 1037–1040. https://doi.org/10.1038/ejcn.2008.81

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. New York: NY: Routledge Academic.

Cohen, P., Cohen, J., Kasen, S., Velez, C. N., Hartmark, C., Johnson, J., … Streuning, E. L. (1993). An Epidemiological Study of Disorders in Late Childhood and Adolescence—I. Age- and Gender-Specific Prevalence. *Journal of Child Psychology and Psychiatry*, *34*(6), 851–867. https://doi.org/10.1111/j.1469-7610.1993.tb01094.x

Cole, G. M., & Frautschy, S. A. (2010). DHA May Prevent Age-Related Dementia. *The Journal of Nutrition*, *140*(4), 869–874. https://doi.org/10.3945/jn.109.113910

Conklin, S. M., Gianaros, P. J., Brown, S. M., Yao, J. K., Hariri, A. R., Manuck, S. B., & Muldoon, M. F. (2007). Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neuroscience Letters*, *421*(3), 209–212. https://doi.org/10.1016/j.neulet.2007.04.086

Conrad, C. D. (2008). Chronic stress-induced hippocampal vulnerability: The glucocorticoid vulnerability hypothesis. *Reviews in the Neurosciences*, *19*(6), 395–411. https://doi.org/10.1515/REVNEURO.2008.19.6.395

Cook, R. L., Parker, H. M., Donges, C. E., O'Dwyer, N. J., Cheng, H. L., Steinbeck, K. S., … O'Connor, H. T. (2019). Omega-3 polyunsaturated fatty acids status and cognitive function in young women. *Lipids in Health and Disease*, *18*(1). https://doi.org/10.1186/s12944-019-1143-z

Cooper, R. E., Tye, C., Kuntsi, J., Vassos, E., & Asherson, P. (2015). Omega-3 polyunsaturated fatty acid supplementation and cognition: A systematic review and meta-analysis. *Journal of Psychopharmacology*, *29*(7), 753–763. https://doi.org/10.1177/0269881115587958

Cornu, C., Mercier, C., Ginhoux, T., Masson, S., Mouchet, J., Nony, P., … Revol, O. (2018). A double-blind placebo-controlled randomised trial of omega-3 supplementation in children with moderate ADHD symptoms. *European Child and Adolescent Psychiatry*, *27*(3), 377–384. https://doi.org/10.1007/s00787-017-1058-z

Costello, E. J., Egger, H., & Angold, A. (2005). 10-Year research update review: The epidemiology of child and adolescent psychiatric disorders: I. Methods and public health burden. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*(10), 972–986. https://doi.org/10.1097/01.chi.0000172552.41596.6f

Costello, E. J., Erkanli, A., & Angold, A. (2006). Is there an epidemic of child or adolescent depression? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*(12), 1263–1271. https://doi.org/10.1111/j.1469-7610.2006.01682.x

Costello, E. J., He, J., Sampson, N. A., Kessler, R. C., & Merikangas, K. R. (2014). Services for Adolescents With Psychiatric Disorders: 12-Month Data From the National Comorbidity Survey–Adolescent. *Psychiatric Services*, *65*(3), 359–366. https://doi.org/10.1176/appi.ps.201100518

Costello, E. J., Mustillo, S., Keeler, G., & Angold, A. (2004). Prevalence of psychiatric disorders in childhood and adolescence. In *Mental Health Services: A Public Health Perspective* (pp. 111–128).

Coti Bertrand, P., O'Kusky, J. R., & Innis, S. M. (2006). Maternal Dietary (n-3) Fatty Acid Deficiency Alters Neurogenesis in the Embryonic Rat Brain. *The Journal of Nutrition*, *136*(6), 1570–1575. https://doi.org/10.1093/jn/136.6.1570

Crippa, A., Tesei, A., Sangiorgio, F., Salandi, A., Trabattoni, S., Grazioli, S., … Nobile, M. (2019). Behavioral and cognitive effects of docosahexaenoic acid in drug-naïve children with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled clinical trial. *European Child and Adolescent Psychiatry*, *28*(4), 571–583. https://doi.org/10.1007/s00787-018-1223-z

Curry, J., Silva, S., Rohde, P., Ginsburg, G., Kratochvil, C., Simons, A., … March, J. (2011). Recovery and recurrence following treatment for adolescent major depression. *Archives of General Psychiatry*, *68*(3), 263–270. https://doi.org/10.1001/archgenpsychiatry.2010.150

Cusick, S. E., & Georgieff, M. K. (2016). The role of nutrition in brain development: The golden opportunity of the "first 1000 days." *Journal of Pediatrics*, *175*, 16–21. https://doi.org/10.1016/j.jpeds.2016.05.013

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*(1), 46–56. https://doi.org/10.1038/nrn2297

Darcey, V. L., McQuaid, G. A., Fishbein, D. H., & VanMeter, J. W. (2019). Dietary long-chain omega-3 fatty acids are related to impulse control and anterior cingulate function in adolescents. *Frontiers in Neuroscience*, *13*(JAN). https://doi.org/10.3389/fnins.2018.01012

Deeks, J. J., Higgins, J. P. T., & Altman, D. G. (editors). (2006). Chapter 9: Analysing data and undertaking meta-analyses. In J. P. T. Higgins & S. Green (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Retrieved from http://handbook.cochrane.org/

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test – second edition. Adult version. Manual. Test*. Pearson.

DeMar, J. C., Ma, K., Bell, J. M., Igarashi, M., Greenstein, D., & Rapoport, S. I. (2006). One generation of n-3 polyunsaturated fatty acid deprivation increases depression and aggression test scores in rats. *Journal of Lipid Research*, *47*(1), 172–180.

https://doi.org/10.1194/jlr.M500362-JLR200

Demmelmair, H., Øyen, J., Pickert, T., Rauh-Pfeiffer, A., Stormark, K. M., Graff, I. E., … Koletzko, B. (2019). The effect of Atlantic salmon consumption on the cognitive performance of preschool children – A randomized controlled trial. *Clinical Nutrition*, *38*(6), 2558–2568. https://doi.org/10.1016/j.clnu.2018.11.031

Deng, W., Aimone, J. B., & Gage, F. H. (2010). New neurons and new memories: How does adult hippocampal neurogenesis affect learning and memory? *Nature Reviews Neuroscience*, *11*(5), 339–350. https://doi.org/10.1038/nrn2822

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*, *7*(3), 177–188. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3802833

Devlin, A. M., Chau, C. M. Y., Dyer, R., Matheson, J., McCarthy, D., Yurko-Mauro, K., … Grunau, R. E. (2017). Developmental Outcomes at 24 Months of Age in Toddlers Supplemented with Arachidonic Acid and Docosahexaenoic Acid: Results of a Double Blind Randomized, Controlled Trial. *Nutrients*, *9*(9). https://doi.org/10.3390/nu9090975

Din, J. N., Newby, D. E., & Flapan, A. D. (2004). Omega 3 fatty acids and cardiovascular disease—fishing for a natural treatment. *Bmj*, *328*(7430), 30. https://doi.org/10.1136/bmj.328.7430.30

Dolean, D., & Cãlugãr, A. (2020). How reliably can we measure a child's true iq? Socio-economic status can explain most of the inter-ethnic differences in general non-verbal abilities. *Frontiers in Psychology*, *11*. https://doi.org/10.3389/fpsyg.2020.02000

Drover, J., Hoffman, D. R., Castañeda, Y. S., Morale, S. E., & Birch, E. E. (2009). Three randomized controlled trials of early long-chain polyunsaturated fatty acid supplementation on means-end problem solving in 9-Month-olds. *Child Development*, *80*(5), 1376–1384. https://doi.org/10.1111/j.1467-8624.2009.01339.x

Duffy, S. L., Lagopoulos, J., Cockayne, N., Lewis, S. J. G., Hickie, I. B., Hermens, D. F., & Naismith, S. L. (2015). The effect of 12-wk ω-3 fatty acid supplementation on in vivo thalamus glutathione concentration in patients "at risk" for major depression. *Nutrition*, *31*(10), 1247–1254. https://doi.org/10.1016/j.nut.2015.04.019

Duman, R. S., & Monteggia, L. M. (2006). A Neurotrophic Model for Stress-Related Mood Disorders. *Biological Psychiatry*, *59*(12), 1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013

Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry*, *64*(3), 327–337. https://doi.org/10.1001/archpsyc.64.3.327

Dunn, V., & Goodyer, I. M. (2006). Longitudinal investigation into childhood- and adolescence-onset depression: Psychiatric outcome in early adulthood. *British Journal of Psychiatry*, *188*(MAR.), 216–222. https://doi.org/10.1192/bjp.188.3.216

Dyall, S. C. (2015). Long-chain omega-3 fatty acids and the brain: A review of the independent and shared effects of EPA, DPA and DHA. *Frontiers in Aging Neuroscience*, *7*(APR). https://doi.org/10.3389/fnagi.2015.00052

Edwards, R., Peet, M., Shay, J., & Horrobin, D. (1998). Depletion of docosahexaenoic acid in red blood cell membranes of depressive patients. *Biochemical Society Transactions*, *26*(2). https://doi.org/10.1042/bst026s142

Eilander, A., Hundscheid, D. C., Osendarp, S. J., Transler, C., & Zock, P. L. (2007). Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: A review of human studies. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *76*(4), 189–203. https://doi.org/10.1016/j.plefa.2007.01.003

Eker, C., & Gonul, A. S. (2010). Volumetric MRI studies of the hippocampus in major depressive disorder: Meanings of inconsistency and directions for future research. *World Journal of Biological Psychiatry*, *11*(1), 19–35. https://doi.org/10.3109/15622970902737998

Emery, S., Häberling, I., Berger, G., Walitza, S., Schmeck, K., Albert, T., … Drechsler, R. (2020). Omega-3 and its domain-specific effects on cognitive test performance in youths: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *112*, 420–436. https://doi.org/10.1016/j.neubiorev.2020.02.016

Erskine, H. E., Moffitt, T. E., Copeland, W. E., Costello, E. J., Ferrari, A. J., Patton, G., … Scott, J. G. (2015). A heavy burden on young minds: The global burden of mental and substance use disorders in children and youth. *Psychological Medicine*, *45*(7), 1561–1563. https://doi.org/10.1017/S0033291714002888

Etkin, A., Patenaude, B., Song, Y. J. C., Usherwood, T., Rekshan, W., Schatzberg, A. F., … Williams, L. M. (2015). A Cognitive–Emotional Biomarker for Predicting Remission with Antidepressant Medications: A Report from the iSPOT-D Trial. *Neuropsychopharmacology*, *40*(6), 1332–1342. https://doi.org/10.1038/npp.2014.333

European Food Safety Authority The Panel on Dietetic Products Nutrition and Allergies on a request from Mead Johnson Nutritionals. (2009). DHA and ARA and visual development - Scientific substantiation of a health claim related to docosahexaenoic acid (DHA) and arachidonic acid (ARA) and visual development pursuant to Article14 of Regulation (EC) No 1924/2006. *EFSA Journal*, *7*(2), 941. https://doi.org/10.2903/j.efsa.2009.941

Fang, M., Li, X., Qian, H., Zeng, K., & Ye, M. (2017). ω -3PUFAs Prevent MK-801-induced Cognitive Impairment in Schizophrenic Rats via the CREB / BDNF / TrkB Pathway *. *J Huanzong Univ Sci Technol*, *37*(4), 491–495. https://doi.org/10.1007/s11596-017-1762-4

Fedorova, I., & Salem, N. (2006). Omega-3 fatty acids and rodent behavior. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *75*(4–5), 271–289. https://doi.org/10.1016/j.plefa.2006.07.006

Fields, J. A., Ferman, T. J., Boeve, B. F., & Smith, G. E. (2011). Neuropsychological assessment of patients with dementing illness. *Nature Reviews Neurology*, *7*(12), 677–687. https://doi.org/10.1038/nrneurol.2011.173

Fletcher, J. M. (2008). Adolescent depression: Diagnosis, treatment, and educational

attainment. *Health Economics*, *17*(11), 1215–1235. https://doi.org/10.1002/hec.1319

Fotuhi, M., Mohassel, P., & Yaffe, K. (2009). Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: A complex association. *Nature Clinical Practice Neurology*, *5*(3), 140–152. https://doi.org/10.1038/ncpneuro1044

Freeman, M. P., & Rapaport, M. H. (2011). Omega-3 fatty acids and depression: From cellular mechanisms to clinical care. *Journal of Clinical Psychiatry*, *72*(2), 258–259. https://doi.org/10.4088/JCP.11ac06830

Fristad, M. A., Vesco, A. T., Young, A. S., Healy, K. Z., Nader, E. S., Gardner, W., … Arnold, L. E. (2019). Pilot Randomized Controlled Trial of Omega-3 and Individual–Family Psychoeducational Psychotherapy for Children and Adolescents With Depression. *Journal of Clinical Child and Adolescent Psychology*, *48*(sup1), S105–S118. https://doi.org/10.1080/15374416.2016.1233500

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jäger, M., Kümmler, P., … Meisenzahl, E. M. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry & Neuroscience : JPN*, *31*(5), 316–323. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1557684

Gawrisch, K., Eldho, N. V., & Holte, L. L. (2003). The structure of DHA in phospholipid membranes. *Lipids*, *38*(4), 445–452. https://doi.org/10.1007/s11745-003-1082-0

Ge, R., Torres, I., Brown, J. J., Gregory, E., McLellan, E., Downar, J. H., … Vila-Rodriguez, F. (2019). Functional disconnectivity of the hippocampal network and neural correlates of memory impairment in treatment-resistant depression. *Journal of Affective Disorders*, *253*, 248–256. https://doi.org/10.1016/j.jad.2019.04.096

Ghio, L., Gotelli, S., Marcenaro, M., Amore, M., & Natta, W. (2014). Duration of untreated illness and outcomes in unipolar depression: A systematic review and meta-analysis. *Journal of Affective Disorders*, *152–154*(1), 45–51. https://doi.org/10.1016/j.jad.2013.10.002

Goodall, J., Fisher, C., Hetrick, S., Phillips, L., Parrish, E. M., & Allott, K. (2018). Neurocognitive Functioning in Depressed Young People: A Systematic Review and Meta-Analysis. *Neuropsychology Review*, *28*(2), 216–231. https://doi.org/10.1007/s11065-018-9373-9

Gorjão, R., Azevedo-Martins, A. K., Rodrigues, H. G., Abdulkader, F., Arcisio-Miranda, M., Procopio, J., & Curi, R. (2009). Comparative effects of DHA and EPA on cell function. *Pharmacology and Therapeutics*, *122*(1), 56–64. https://doi.org/10.1016/j.pharmthera.2009.01.004

Gorwood, P., Corruble, E., Falissard, B., & Goodwin, G. M. (2008). Toxic effects of depression on brain function: Impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *American Journal of Psychiatry*, *165*(6), 731–739. https://doi.org/10.1176/appi.ajp.2008.07040574

Gould, J. F., Smithers, L. G., & Makrides, M. (2013). The effect of maternal omega-3 (n23) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: A systematic review and meta-analysis of randomized controlled trials1-3.

American Journal of Clinical Nutrition, *97*(3), 531–544. https://doi.org/10.3945/ajcn.112.045781

Groen, G., & Petermann, F. (2013). Depressive Störungen. In F. Petermann (Ed.), *Lehrbuch der Klinischen Kinderpsychologie* (7th ed., pp. 39–458). Göttingen: Hogrefe.

Grosso, G., Galvano, F., Marventano, S., Malaguarnera, M., Bucolo, C., Drago, F., & Caraci, F. (2014). Omega-3 fatty acids and depression: Scientific evidence and biological mechanisms. *Oxidative Medicine and Cellular Longevity*, *2014*. https://doi.org/10.1155/2014/313570

Grosso, G., Pajak, A., Marventano, S., Castellano, S., Galvano, F., Bucolo, C., … Caraci, F. (2014). Role of omega-3 fatty acids in the treatment of depressive disorders: A comprehensive meta-analysis of randomized clinical trials. *PLoS ONE*, *9*(5). https://doi.org/10.1371/journal.pone.0096905

Guixà-González, R., Javanainen, M., Gómez-Soler, M., Cordobilla, B., Domingo, J. C., Sanz, F., … Selent, J. (2016). Membrane omega-3 fatty acids modulate the oligomerisation kinetics of adenosine A2A and dopamine D2 receptors. *Scientific Reports*, *6*. https://doi.org/10.1038/srep19839

Günther, T., Holtkamp, K., Jolles, J., Herpertz-Dahlmann, B., & Konrad, K. (2004). Verbal memory and aspects of attentional control in children and adolescents with anxiety disorders or depressive disorders. *Journal of Affective Disorders*, *82*(2), 265–269. https://doi.org/10.1016/j.jad.2003.11.004

Guo, Y., Nilsson, M. E., Heiligenstein, J., Wilson, M. G., & Emslie, G. (2006). An exploratory factor analysis of the Children's Depression Rating Scale-Revised. *Journal of Child and Adolescent Psychopharmacology*, *16*(4), 482–491. https://doi.org/10.1089/cap.2006.16.482

Gygi, J. T., Hagmann-von Arx, P., Schweizer, F., & Grob, A. (2017). The predictive validity of four intelligence tests for school grades: A small sample longitudinal study. *Frontiers in Psychology*, *8*(MAR). https://doi.org/10.3389/fpsyg.2017.00375

Häberling, I., Berger, G., Schmeck, K., Held, U., & Walitza, S. (2019). Omega-3 Fatty Acids as a Treatment for Pediatric Depression. A Phase III, 36 Weeks, Multi-Center, Double-Blind, Placebo-Controlled Randomized Superiority Study. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00863

Hagmann-von Arx, P., & Grob, A. (2014). RIAS. Reynolds Intellectual Assessment Scales and Screening. Deutschsprachige Adaptation der Reynolds Intellectual Assessment Scales (RIAS) & des Reynolds Intellectual Screening Test (RIST) von Cecil R. Reynolds und Randy W. Kamphaus.

Hallahan, B., Ryan, T., Hibbeln, J. R., Murray, I. T., Glynn, S., Ramsden, C. E., … Davis, J. M. (2016). Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. *British Journal of Psychiatry*, *209*(3), 192–201. https://doi.org/10.1192/bjp.bp.114.160242

Hamilton, J. A., Hillard, C. J., Spector, A. A., & Watkins, P. A. (2007). Brain Uptake and Utilization of Fatty Acids, Lipids and Lipoproteins: Application to Neurological

Disorders. *Journal of Molecular Neuroscience*, *33*(1), 2–11. https://doi.org/10.1007/s12031-007-0060-1

Hammar, Å., & Årdal, G. (2009). Cognitive functioning in major depression - A summary. *Frontiers in Human Neuroscience*, *3*(SEP). https://doi.org/10.3389/neuro.09.026.2009

Handeland, K., Øyen, J., Skotheim, S., Graff, I. E., Baste, V., Kjellevold, M., … Stormark, K. M. (2017). Fatty fish intake and attention performance in 14-15 year old adolescents: FINS-TEENS - A randomized controlled trial. *Nutrition Journal*, *16*(1). https://doi.org/10.1186/s12937-017-0287-9

Hanebutt, F. L., Demmelmair, H., Schiessl, B., Larqué, E., & Koletzko, B. (2008). Long-chain polyunsaturated fatty acid (LC-PUFA) transfer across the placenta. *Clinical Nutrition*, *27*(5), 685–693. https://doi.org/10.1016/j.clnu.2008.05.010

Hanson, S., Thorpe, G., Winstanley, L., Abdelhamid, A. S., Hooper, L., Abdelhamid, A., … Winstanley, L. (2020). Omega-3, omega-6 and total dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials. *British Journal of Cancer*, *122*(8), 1260–1270. https://doi.org/10.1038/s41416-020-0761-6

Harbild, H. L., Harsløf, L. B., Christensen, J. H., Kannass, K. N., & Lauritzen, L. (2013). Fish oil-supplementation from 9 to 12 months of age affects infant attention in a free-play test and is related to change in blood pressure. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, *89*(5), 327–333. https://doi.org/10.1016/j.plefa.2013.08.007

Harris, W. S. (2010). Omega-3 Fatty Acids. In P. M. Coates, J. M. Betz, M. R. Blackman, G. M. Cragg, M. Levine, J. Moss, & J. D. White (Eds.), *Encyclopedia of Dietary Supplements* (2nd Editio, pp. 577–586). London and New York: Informa Healthcare.

Harris, W. S., & Klurfeld, D. M. (2011). Twentieth-century trends in essential fatty acid intakes and the predicted omega-3 index: Evidence versus estimates. *American Journal of Clinical Nutrition*, *93*(5), 907–908. https://doi.org/10.3945/ajcn.111.014365

Harris, W. S., von Schacky, C., & Park, Y. (2013). Standardizing methods for assessing omega-3 fatty acid biostatus. In *The Omega-3 Fatty Acid Deficiency Syndrome: Opportunities for Disease Prevention* (pp. 385–398).

Harvey, P. D. (2019). Domains of cognition and their assessment. *Dialogues in Clinical Neuroscience*, *21*(3), 227–237. https://doi.org/10.31887/DCNS.2019.21.3/pharvey

Harvey, P. D., Aslan, M., Du, M., Zhao, H., Siever, L. J., Pulver, A., … Concato, J. (2016). Factor structure of cognition and functional capacity in two studies of schizophrenia and bipolar disorder: Implications for genomic studies. *Neuropsychology*, *30*(1), 28–39. https://doi.org/10.1037/neu0000245

Hasselbalch, B. J., Knorr, U., Hasselbalch, S. G., Gade, A., & Kessing, L. V. (2013). The cumulative load of depressive illness is associated with cognitive function in the remitted state of unipolar depressive disorder. *European Psychiatry*, *28*(6), 349–355. https://doi.org/10.1016/j.eurpsy.2012.03.004

Hasselbalch, Bo Jacob, Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: A systematic review. *Journal of Affective*

Disorders, *134*(1–3), 20–31. https://doi.org/10.1016/j.jad.2010.11.011

Haubner, L., Sullivan, J., Ashmeade, T., Saste, M., Wiener, D., & Carver, J. (2007). The effects of maternal dietary docosahexaenoic acid intake on rat pup myelin and the auditory startle response. *Developmental Neuroscience*, *29*(6), 460–467. https://doi.org/10.1159/000107047

Helmstaedter, C., & Durwen, H. F. (1990). Vlmt: Verbaler Lern- Und Merkfahigkeitstest. Ein Praktikables Und Differenziertes Instrumentarium Zur Prufung Der Verbalen Gedachtnisleistungen. *Schweizer Archiv Fur Neurologie Und Psychiatrie*, *141*(1), 21–30.

Herter-Aeberli, I., Graf, C., Vollenweider, A., Häberling, I., Srikanthan, P., Hersberger, M., … Mathis, D. (2019). Validation of a food frequency questionnaire to assess intake of n-3 polyunsaturated fatty acids in switzerland. *Nutrients*, *11*(8). https://doi.org/10.3390/nu11081863

Higgins, J. P. T., Altman, D. G., & Sterne, J. A. C. (editors). (2006). Chapter 8: Assessing risk of bias in included studies. In J. P. T. Higgins & S. Green (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Retrieved from www.handbook.cochrane.org

Higgins, J. P. T., Deeks, J. J., & Altman, D. G. (editors). (2006). Chapter 16: Special Topics in statistics. In J. P. T. Higgins & S. Green (Eds.), *Cochrane Handbook for Systematic Reviews and Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Retrieved from www.handbook.cochrane.org

Higgins, J. P. T., & Green, S. (Eds.). (2006). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Retrieved from www.handbook.cochrane.org.

Hirayama, S., Hamazaki, T., & Terasawa, K. (2004). Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - A placebo-controlled double-blind study. *European Journal of Clinical Nutrition*, *58*(3), 467–473. https://doi.org/10.1038/sj.ejcn.1601830

Holsboer, F. (2013). The Corticosteroid receptor hypothesis of depression. *Depression: The Science of Mental Health*, *6*, 219–244.

Horowitz, M. A., Zunszain, P. A., Anacker, C., Musaelyan, K., & Pariante, C. M. (2013). Glucocorticoids and inflammation: A double-headed sword in depression?: How do neuroendocrine and inflammatory pathways interact during stress to contribute to the pathogenesis of depression? *Inflammation in Psychiatry*, *28*, 127–143. https://doi.org/10.1159/000343980

Hort, J., Valis, M., Angelucci, F., Pistollato, F., Cano, S. S., Elio, I., … Boza-serrano, A. A. E. W. G. M. B. A. (2020). The gut-brain axis in Alzheimer's disease and omega-3. A critical overview of clinical trials. *Nutrients*, *10*(3), 1006–1023. Retrieved from http://dx.doi.org/10.1016/j.phrs.2017.12.009

Howell, D. C. (2012). *Statistical Methods for Psychology* (7th ed.). Belmont, CA: Wadsworth Cengage Learning.

Igarashi, M., Santos, R. A., & Cohen-Cory, S. (2015). Impact of maternal n-3 polyunsaturated fatty acid deficiency on dendritic arbor morphology and connectivity of developing xenopus laevis central neurons in vivo. *The Journal of Neuroscience*, *35*(15), 6079–6092. https://doi.org/10.1523/JNEUROSCI.4102-14.2015

Innis, S. M. (2008). Dietary omega 3 fatty acids and the developing brain. *Brain Research*, *1237*, 35–43. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008464567

Iob, E., Kirschbaum, C., & Steptoe, A. (2019). Persistent depressive symptoms, HPA-axis hyperactivity, and inflammation: the role of cognitive-affective and somatic symptoms. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0501-6

Itua, I., & Naderali, E. K. (2010). Review: Omega-3 and Memory Function: To Eat or Not To Eat. *American Journal of Alzheimer's Disease & Other Dementiasr*, *25*(6), 479–482. https://doi.org/10.1177/1533317510376943

Iverson, G. L., & Lam, R. W. (2013). Rapid screening for perceived cognitive impairment in major depressive disorder. *Annals of Clinical Psychiatry*, *25*(2), 135–140.

Janssen, C. I. F., & Kiliaan, A. J. (2014). Long-chain polyunsaturated fatty acids (LCPUFA) from genesis to senescence: The influence of LCPUFA on neural development, aging, and neurodegeneration. *Progress in Lipid Research*, *53*(1), 1–17. https://doi.org/10.1016/j.plipres.2013.10.002

Jernerén, F., Cederholm, T., Refsum, H., Smith, A. D., Turner, C., Palmblad, J., … Freund-Levi, Y. (2019). Homocysteine status modifies the treatment effect of omega-3 fatty acids on cognition in a randomized clinical trial in mild to moderate Alzheimer's disease: The OmegAD Study. *Journal of Alzheimer's Disease*, *69*(1), 189–197. https://doi.org/10.3233/JAD-181148

Jiao, J., Li, Q., Chu, J., Zeng, W., Yang, M., & Zhu, S. (2014). Effect of n-3 PUFA supplementation on cognitive function throughout the life span from infancy to old age: A systematic review and meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition*, *100*(6), 1422–1436. https://doi.org/10.3945/ajcn.114.095315

Joffre, C., Nadjar, A., Lebbadi, M., Calon, F., & Laye, S. (2014). n-3 LCPUFA improves cognition: The young, the old and the sick. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *91*(1–2), 1–20. https://doi.org/10.1016/j.plefa.2014.05.001

Johnson, M., Fransson, G., Östlund, S., Areskoug, B., & Gillberg, C. (2017). Omega 3/6 fatty acids for reading in children: a randomized, double-blind, placebo-controlled trial in 9-year-old mainstream schoolchildren in Sweden. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *58*(1), 83–93. https://doi.org/10.1111/jcpp.12614

Johnson, S. B., Blum, R. W., & Giedd, J. N. (2009). Adolescent Maturity and the Brain: The Promise and Pitfalls of Neuroscience Research in Adolescent Health Policy. *Journal of Adolescent Health*, *45*(3), 216–221. https://doi.org/10.1016/j.jadohealth.2009.05.016

Jones, P. J. H., & Rideout, T. (2012). Lipids, sterols, and their metabolites. In *Modern*

Nutrition in Health and Disease: Eleventh Edition (pp. 65–87).

Kalmijn, S., Van Boxtel, M. P. J., Ocké, M., Verschuren, W. M. M., Kromhout, D., & Launer, L. J. (2004). Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology*, *62*(2), 275–280. https://doi.org/10.1212/01.WNL.0000103860.75218.A5

Karr, J. E., Alexander, J. E., & Winningham, R. G. (2011). Omega-3 polyunsaturated fatty acids and cognition throughout the lifespan: a review. *Nutritional Neuroscience*, *14*(5), 216–225. https://doi.org/10.1179/1476830511Y.0000000012

Karr, J. E., Grindstaff, T. R., & Alexander, J. E. (2012). Omega-3 polyunsaturated fatty acids and cognition in a college-aged population. *Experimental and Clinical Psychopharmacology*, *20*(3), 236–242.

Katakura, M., Hashimoto, M., Okui, T., Shahdat, H. M., Matsuzaki, K., & Shido, O. (2013). Omega-3 polyunsaturated fatty acids enhance neuronal differentiation in cultured rat neural stem cells. *Stem Cells International*. https://doi.org/10.1155/2013/490476

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kawakita, E., Hashimoto, M., & Shido, O. (2006). Docosahexaenoic acid promotes neurogenesis in vitro and in vivo. *Neuroscience*, *139*(3), 991–997. https://doi.org/10.1016/j.neuroscience.2006.01.021

Kean, J. D., Sarris, J., Scholey, A., Silberstein, R., Downey, L. A., & Stough, C. (2017). Reduced inattention and hyperactivity and improved cognition after marine oil extract (PCSO-524®) supplementation in children and adolescents with clinical and subclinical symptoms of attention-deficit hyperactivity disorder (ADHD): a randomised, double-b. *Psychopharmacology*, *234*(3), 403–420. https://doi.org/10.1007/s00213-016-4471-y

Kennedy, D. O., Jackson, P. A., Elliott, J. M., Scholey, A. B., Robertson, B. C., Greer, J., … Haskell, C. F. (2009). Cognitive and mood effects of 8 weeks' supplementation with 400 mg or 1000 mg of the omega-3 essential fatty acid docosahexaenoic acid (DHA) in healthy children aged 10–12 years. *Nutritional Neuroscience*, *12*(2), 48–56. https://doi.org/10.1016/j.geb.2011.05.014

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Üstün, T. B. (2007). Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry*, *20*(4), 359–364. https://doi.org/10.1097/YCO.0b013e32816ebc8c

Kessler, R. C., & Bromet, E. J. (2013). The Epidemiology of Depression Across Cultures. *Annual Review of Public Health*, *34*(1), 119–138. https://doi.org/10.1146/annurev-publhealth-031912-114409

Kessler, R. C., Sampson, N. A., Berglund, P., Gruber, M. J., Al-Hamzawi, A., Andrade, L., … Wilcox, M. A. (2015). Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiology and*

Psychiatric Sciences, *24*(3), 210–226. https://doi.org/10.1017/S2045796015000189

Kessler, R. C., & Walters, E. E. (1998). Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depression and Anxiety*, *7*(1), 3–14. https://doi.org/10.1002/(SICI)1520-6394(1998)7:1<3::AID-DA2>3.0.CO;2-F

Khodarahm, M., & Azadbakht, L. (2016). Dietary fat intake and functional dyspepsia. *Advanced Biomedical Research*, *5*(1), 76. https://doi.org/10.4103/2277-9175.180988

Kim, H. Y., Akbar, M., Lau, A., & Edsall, L. (2000). Inhibition of neuronal apoptosis by docosahexaenoic acid (22:6n-3): Role of phosphatidylserine in antiapoptotic effect. *Journal of Biological Chemistry*, *275*(45), 35215–35223. https://doi.org/10.1074/jbc.M004446200

Kim, Y. K., Na, K. S., Myint, A. M., & Leonard, B. E. (2016). The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *64*, 277–284. https://doi.org/10.1016/j.pnpbp.2015.06.008

Kirby, A., Woodward, A., Jackson, S., Wang, Y., & Crawford, M. A. (2010). A double-blind, placebo-controlled study investigating the effects of omega-3 supplementation in children aged 8-10 years from a mainstream school population. *Research in Developmental Disabilities*, *31*(3), 718–730.

Knight, M. J., & Baune, B. T. (2018). Cognitive dysfunction in major depressive disorder. *Current Opinion in Psychiatry*, *31*(1), 26–31. https://doi.org/10.1097/YCO.0000000000000378

Knight, M. J., Lyrtzis, E., & Baune, B. T. (2020). The association of cognitive deficits with mental and physical Quality of Life in Major Depressive Disorder. *Comprehensive Psychiatry*, *97*, 152147. https://doi.org/10.1016/j.comppsych.2019.152147

Knochel, C., Voss, M., Gruter, F., S. Alves, G., Matura, S., Sepanski, B., … Oertel-Knochel, V. (2015). Omega 3 Fatty Acids: Novel Neurotherapeutic Targets for Cognitive Dysfunction in Mood Disorders and Schizophrenia? *Current Neuropharmacology*, *13*(5), 663–680. https://doi.org/10.2174/1570159x13666150630173047

Köhler, A., Bittner, D., Löw, A., & Von Schacky, C. (2010). Effects of a convenience drink fortified with n-3 fatty acids on the n-3 index. *British Journal of Nutrition*, *104*(5), 729–736. https://doi.org/10.1017/S0007114510001054

Kolb, B., Mychasiuk, R., Muhammad, A., Li, Y., Frost, D. O., & Gibb, R. (2012). Experience and the developing prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(SUPPL.2), 17186–17196. https://doi.org/10.1073/pnas.1121251109

Koletzko, B., Lien, E., Agostoni, C., Bohles, H., Campoy, C., Cetin, I., … Forsyth, S. (2008). The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: Review of current knowledge and consensus recommendations. *Journal of Perinatal Medicine*, *36*(1), 5–14. https://doi.org/10.1515/JPM.2008.001

Kraus, C., Kadriu, B., Lanzenberger, R., Zarate, C. A., & Kasper, S. (2019). Prognosis and improved outcomes in major depression: a review. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0460-3

Krieger, V., & Amador-Campos, J. A. (2018). Assessment of executive function in ADHD adolescents: contribution of performance tests and rating scales. *Child Neuropsychology*, *24*(8), 1063–1087. https://doi.org/10.1080/09297049.2017.1386781

Krishnan, S., Watkins, K. E., & Bishop, D. V. M. (2017). The effect of recall, reproduction, and restudy on word learning: A pre-registered study. *BMC Psychology*, *5*(1). https://doi.org/10.1186/s40359-017-0198-8

Krist, H., Kunter, M., Nückles, M., Pinquart, M., & Seidel, T. (2016). Testbesprechung. *Zeitschrift Für Entwicklungspsychologie Und Pädagogische Psychologie*, *48*(1), 50–55.

Kuipers, R. S., Luxwolda, M. F., Offringa, P. J., Rudi Boersma, E., Dijck-Brouwer, D. A. J., & Muskiet, F. A. J. (2012). Fetal intrauterine whole body linoleic, arachidonic and docosahexaenoic acid contents and accretion rates. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *86*(1–2), 13–20. https://doi.org/10.1016/j.plefa.2011.10.012

Kunugi, H., Ida, I., Owashi, T., Kimura, M., Inoue, Y., Nakagawa, S., … Mikuni, M. (2006). Assessment of the dexamethasone/CRH test as a state-dependent marker for hypothalamic-pituitary-adrenal (HPA) axis abnormalities in major depressive episode: A multicenter study. *Neuropsychopharmacology*, *31*(1), 212–220. https://doi.org/10.1038/sj.npp.1300868

Kuratko, C. N., Barrett, E. C., Nelson, E. B., & Salem, N. (2013). The relationship of docosahexaenoic acid (DHA) with learning and behavior in healthy children: A review. *Nutrients*, *5*(7), 2777–2810. https://doi.org/10.3390/nu5072777

Labrousse, V. F., Nadjar, A., Joffre, C., Costes, L., Aubert, A., Grégoire, S., … Layé, S. (2012). Short-Term Long Chain Omega3 Diet Protects from Neuroinflammatory Processes and Memory Impairment in Aged Mice. *PLoS ONE*, *7*(5), e36861. https://doi.org/10.1371/journal.pone.0036861

Ladouceur, C. D., Slifka, J. S., Dahl, R. E., Birmaher, B., Axelson, D. A., & Ryan, N. D. (2012). Altered error-related brain activity in youth with major depression. *Developmental Cognitive Neuroscience*, *2*(3), 351–362. https://doi.org/10.1016/j.dcn.2012.01.005

Lahr, D., Beblo, T., & Hartje, W. (2007). Cognitive performance and subjective complaints before and after remission of major depression. *Cognitive Neuropsychiatry*, *12*(1), 25–45. https://doi.org/10.1080/13546800600714791

Larrieu, T., Hilal, L. M., Fourrier, C., De Smedt-Peyrusse, V., Sans, N., Capuron, L., & Layé, S. (2014). Nutritional omega-3 modulates neuronal morphology in the prefrontal cortex along with depression-related behavior through corticosterone secretion. *Translational Psychiatry*, *4*(9). https://doi.org/10.1038/tp.2014.77

Larrieu, T., Madore, C., Joffre, C., & Layé, S. (2012). Nutritional n-3 polyunsaturated fatty acids deficiency alters cannabinoid receptor signaling pathway in the brain and associated anxiety-like behavior in mice. *Journal of Physiology and Biochemistry*,

68(4), 671–681. https://doi.org/10.1007/s13105-012-0179-6

Lassek, W. D., & Gaulin, S. J. C. (2011). Sex differences in the relationship of dietary fatty acids to cognitive measures in American children. *Frontiers in Evolutionary Neuroscience*, *3*(NOV). https://doi.org/10.3389/fnevo.2011.00005

Lauritzen, L., Brambilla, P., Mazzocchi, A., Harsløf, L., Ciappolino, V., & Agostoni, C. (2016). DHA Effects in Brain Development and Function. *Nutrients*, *8*(1), 6. https://doi.org/10.3390/nu8010006

Lauritzen, L., & Carlson, S. E. (2011). Maternal fatty acid status during pregnancy and lactation and relation to newborn and infant status. *Maternal & Child Nutrition*, *7*(SUPPL. 2), 41–58. https://doi.org/10.1111/j.1740-8709.2011.00303.x

Layé, S. (2010). Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *82*(4–6), 295–303. https://doi.org/10.1016/j.plefa.2010.02.006

Layé, S., Nadjar, A., Joffre, C., & Bazinet, R. P. (2018). Anti-inflammatory effects of omega-3 fatty acids in the brain: Physiological mechanisms and relevance to pharmacology. *Pharmacological Reviews*, *70*(1), 12–38. https://doi.org/10.1124/pr.117.014092

Leaf, P. J., Alegria, M., Cohen, P., Goodman, S. H., Horwitz, S. M., Hoven, C. W., … Regier, D. A. (1996). Mental health service use in the community and schools: results from the four-community MECA Study. Methods for the Epidemiology of Child and Adolescent Mental Disorders Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *35*(7), 889–897. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8768348

Lecrubier, Y. (2007). Widespread underrecognition and undertreatment of anxiety and mood disorders: Results from 3 European studies. *Journal of Clinical Psychiatry*, *68*(SUPPL. 2), 36–41.

Lee, J. H., O'Keefe, J. H., Lavie, C. J., & Harris, W. S. (2009). Omega-3 fatty acids: Cardiovascular benefits, sources and sustainability. *Nature Reviews Cardiology*, *6*(12), 753–758. https://doi.org/10.1038/nrcardio.2009.188

Lee, L. K., Shahar, S., Chin, A.-V., & Yusoff, N. A. M. (2013). Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. *Psychopharmacology*, *225*(3), 605–612. https://doi.org/10.1007/s00213-012-2848-0

Lee, R. S. C., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, *140*(2), 113–124. https://doi.org/10.1016/j.jad.2011.10.023

Lee, S., Lee, J., Choi, J., Kim, Y. W., Ryu, K. W., Kim, Y., & Kim, J. (2018). Dietary n-3 and n-6 polyunsaturated fatty acids, the FADS gene, and the risk of gastric cancer in a Korean population. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-21960-3

Lehner, A., Staub, K., Aldakak, L., Eppenberger, P., Rühli, F., Martin, R. D., & Bender, N. (2020). Impact of omega-3 fatty acid DHA and EPA supplementation in pregnant or

breast-feeding women on cognitive performance of children: systematic review and meta-analysis. *Nutrition Reviews*. https://doi.org/10.1093/nutrit/nuaa060

Leonard, B., & Maes, M. (2012). Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neuroscience and Biobehavioral Reviews*, *36*(2), 764–785. https://doi.org/10.1016/j.neubiorev.2011.12.005

Leutgeb, V., Köchel, A., Lang, L., Koch, J., & Schienle, A. (2015). Effects of omega-3 fatty acids on cognitive, emotional, and social behavioral parameters in kindergarten children: A pilot study . *Kindheit Und Entwicklung*, *24*(2), 86–93. https://doi.org/10.1026/0942-5403/a000164

Li, F., Liu, X., & Zhang, D. (2015). Fish consumption and risk of depression: A meta-analysis. *Journal of Epidemiology and Community Health*, *70*(3), 299–304. https://doi.org/10.1136/jech-2015-206278

Li, K., Huang, T., Zheng, J., Wu, K., & Li, D. (2014). Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor α: A meta-analysis. *PLoS ONE*, *9*(2). https://doi.org/10.1371/journal.pone.0088103

Li, Y., Dai, Q., Ekperi, L. I., Dehal, A., & Zhang, J. (2011). Fish consumption and severely depressed mood, findings from the first national nutrition follow-up study. *Psychiatry Research*, *190*(1), 103–109. https://doi.org/10.1016/j.psychres.2011.05.012

Liao, Y., Xie, B., Zhang, H., He, Q., Guo, L., Subramaniapillai, M., … Mclntyer, R. S. (2019). Efficacy of omega-3 PUFAs in depression: A meta-analysis. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0515-5

Lim, J. H., Oh, I. K., Han, C., Huh, Y. J., Jung, I. K., Patkar, A. A., … Jang, B. H. (2013). Sensitivity of cognitive tests in four cognitive domains in discriminating MDD patients from healthy controls: A meta-analysis. *International Psychogeriatrics*, *25*(9), 1543–1557. https://doi.org/10.1017/S1041610213000689

Lin, P.-Y., Huang, S.-Y., & Su, K.-P. (2010). A Meta-Analytic Review of Polyunsaturated Fatty Acid Compositions in Patients with Depression. *Biological Psychiatry*, *68*(2), 140–147. https://doi.org/10.1016/j.biopsych.2010.03.018

Lotrich, F. E. (2015). Inflammatory cytokine-associated depression. *Brain Research*, *1617*, 113–125. https://doi.org/10.1016/j.brainres.2014.06.032

Lovegrove, J. A., Lovegrove, S. S., Lesauvage, S. V., Brady, L. M., Saini, N., Minihane, A. M., & Williams, C. M. (2004). Moderate fish-oil supplementation reverses low-platelet, long-chain n−3 polyunsaturated fatty acid status and reduces plasma triacylglycerol concentrations in British Indo-Asians. *The American Journal of Clinical Nutrition*, *79*(6), 974–982. https://doi.org/10.1093/ajcn/79.6.974

Luchtman, D. W., & Song, C. (2013). Cognitive enhancement by omega-3 fatty acids from child-hood to old age: Findings from animal and clinical studies. *Neuropharmacology*, *64*, 550–565. https://doi.org/10.1016/j.neuropharm.2012.07.019

Lumley, T., Diehr, P., Emerson, S., & Chen, L. (2002). The importance of the normality assumption in large public health data sets. *Annual Review of Public Health*, *23*, 151–169. https://doi.org/10.1146/annurev.publhealth.23.100901.140546

Maalouf, F. T., Brent, D., Clark, L., Tavitian, L., McHugh, R. M., Sahakian, B. J., & Phillips, M. L. (2011). Neurocognitive impairment in adolescent major depressive disorder: state vs. trait illness markers. *Journal of Affective Disorders*, *133*(3), 625–632. https://doi.org/10.1016/j.jad.2011.04.041

Makrides, M., Neumann, M. A., Simmer, K., & Gibson, R. A. (2000). A critical appraisal of the role of dietary long-chain polyunsaturated fatty acids on neural indices of term infants: A randomized, controlled trial. *Pediatrics*, *105*(1 I), 32–38. https://doi.org/10.1542/peds.105.1.32

Marazziti, D., Consoli, G., Picchetti, M., Carlini, M., & Faravelli, L. (2010). Cognitive impairment in major depression. *European Journal of Pharmacology*, *626*(1), 83–86. https://doi.org/10.1016/j.ejphar.2009.08.046

Martin, D. S. D., Lonergan, P. E., Boland, B., Fogarty, M. P., Brady, M., Horrobin, D. F., … Lynch, M. A. (2002). Apoptotic changes in the aged brain are triggered by interleukin-1β-induced activation of p38 and reversed by treatment with eicosapentaenoic acid. *Journal of Biological Chemistry*, *277*(37), 34239–34246. https://doi.org/10.1074/jbc.M205289200

Martins, J. G. (2009). EPA but Not DHA Appears To Be Responsible for the Efficacy of Omega-3 Long Chain Polyunsaturated Fatty Acid Supplementation in Depression: Evidence from a Meta-Analysis of Randomized Controlled Trials. *Journal of the American College of Nutrition*, *28*(5), 525–542. https://doi.org/10.1080/07315724.2009.10719785

Massaro, M., Scoditti, E., Carluccio, M. A., & De Caterina, R. (2008). Basic mechanisms behind the effects of n-3 fatty acids on cardiovascular disease. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *79*(3–5), 109–115. https://doi.org/10.1016/j.plefa.2008.09.009

Mayes, T. L., Bernstein, I. H., Haley, C. L., Kennard, B. D., & Emslie, G. J. (2010). Psychometric properties of the children's depression rating Scale-Revised in adolescents. *Journal of Child and Adolescent Psychopharmacology*, *20*(6), 513–516. https://doi.org/10.1089/cap.2010.0063

Mazereeuw, G., Lanctôt, K. L., Chau, S. A., Swardfager, W., & Herrmann, N. (2012). Effects of omega-3 fatty acids on cognitive performance: A meta-analysis. *Neurobiology of Aging*, *33*(7). https://doi.org/10.1016/j.neurobiolaging.2011.12.014

McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: A review and synthesis. *Neuropsychology*, *24*(1), 9–34. https://doi.org/10.1037/a0017336

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, *119*(1–3), 1–8.

https://doi.org/10.1016/j.jad.2009.04.022

McGahon, B. M., Martin, D. S. D., Horrobin, D. F., & Lynch, M. A. (1999). Age-related changes in synaptic function: Analysis of the effect of dietary supplementation with ω-3 fatty acids. *Neuroscience*, *94*(1), 305–314. https://doi.org/10.1016/S0306-4522(99)00219-5

McIntyre, R. (2014). Major depressive disorder and cognitive impairment. *Journal of Psychiatry & Neuroscience*, *39*(5), E36–E37. https://doi.org/10.1503/jpn.140050

McIntyre, R. S., Cha, D. S., Soczynska, J. K., Woldeyohannes, H. O., Gallaugher, L. A., Kudlow, P., … Baskaran, A. (2013). Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depression and Anxiety*, *30*(6), 515–527. https://doi.org/10.1002/da.22063

McIntyre, R. S., Xiao, H. X., Syeda, K., Vinberg, M., Carvalho, A. F., Mansur, R. B., … Cha, D. S. (2015). The Prevalence, Measurement, and Treatment of the Cognitive Dimension/Domain in Major Depressive Disorder. *CNS Drugs*, *29*(7), 577–589. https://doi.org/10.1007/s40263-015-0263-x

McNamara, R. K., Able, J., Jandacek, R., Rider, T., Tso, P., Eliassen, J. C., … Adler, C. M. (2010). Docosahexaenoic acid supplementation increases prefrontal cortex activation during sustained attention in healthy boys: a placebo-controlled, dose-ranging, functional magnetic resonance imaging study. *The American Journal of Clinical Nutrition*, *91*(4), 1060–1067. https://doi.org/10.3945/ajcn.2009.28549

McNamara, R. K., Able, J., Liu, Y., Jandacek, R., Rider, T., Tso, P., & Lipton, J. W. (2009). Omega-3 fatty acid deficiency during perinatal development increases serotonin turnover in the prefrontal cortex and decreases midbrain tryptophan hydroxylase-2 expression in adult female rats: Dissociation from estrogenic effects. *Journal of Psychiatric Research*, *43*(6), 656–663. https://doi.org/10.1016/j.jpsychires.2008.09.011

McNamara, R. K., & Carlson, S. E. (2006). Role of omega-3 fatty acids in brain development and function: Potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *75*(4–5), 329–349. https://doi.org/10.1016/j.plefa.2006.07.010

McNamara, R. K., Hahn, C.-G., Jandacek, R., Rider, T., Tso, P., Stanford, K. E., & Richtand, N. M. (2007). Selective Deficits in the Omega-3 Fatty Acid Docosahexaenoic Acid in the Postmortem Orbitofrontal Cortex of Patients with Major Depressive Disorder. *Biological Psychiatry*, *62*(1), 17–24. https://doi.org/10.1016/j.biopsych.2006.08.026

McNamara, R. K., Jandacek, R., Tso, P., Dwivedi, Y., Ren, X., & Pandey, G. N. (2013). Lower docosahexaenoic acid concentrations in the postmortem prefrontal cortex of adult depressed suicide victims compared with controls without cardiovascular disease. *Journal of Psychiatric Research*, *47*(9), 1187–1191. https://doi.org/10.1016/j.jpsychires.2013.05.007

McNamara, R. K., Strimpfel, J., Jandacek, R., Rider, T., Tso, P., Welge, J. A., … DelBello, M. P. (2014). Detection and treatment of long-chain omega-3 fatty acid deficiency in adolescents with SSRI-resistant major depressive disorder. *PharmaNutrition*, *2*(2), 38–

46. https://doi.org/10.1016/j.phanu.2014.02.002

McNamara, R. K., Vannest, J., & Valentine, C. (2015). Role of perinatal long-chain omega-3 fatty acids in cortical circuit maturation: Mechanisms and implications for psychopathology. *World Journal of Psychiatry*, *5*(1), 15. https://doi.org/10.5498/wjp.v5.i1.15

Meldrum, S. J., D'Vaz, N., Simmer, K., Dunstan, J. A., Hird, K., & Prescott, S. L. (2012). Effects of high-dose fish oil supplementation during early infancy on neurodevelopment and language: A randomised controlled trial. *British Journal of Nutrition*, *108*(8), 1443–1454. https://doi.org/10.1017/S0007114511006878

Mensah, F. K., & Kiernan, K. E. (2010). Parents' mental health and children's cognitive and social development: Families in England in the Millennium Cohort Study. *Social Psychiatry and Psychiatric Epidemiology*, *45*(11), 1023–1035. https://doi.org/10.1007/s00127-009-0137-y

Merikangas, K. R., & Avenevoli, S. (2003). Epidemiology of Mood and Anxiety Disorders in Children and Adolescents. In *Textbook in Psychiatric Epidemiology* (pp. 657–704). https://doi.org/10.1002/0471234311.ch24

Merle, B. M. J., Benlian, P., Puche, N., Bassols, A., Delcourt, C., Souied, E. H., & Group, N. A. M. D. T. 2 S. (2014). Circulating omega-3 Fatty acids and neovascular age-related macular degeneration. *Investigative Ophthalmology & Visual Science*, *55*(3), 2010–2019. https://doi.org/https://dx.doi.org/10.1167/iovs.14-13916

Messamore, E., Almeida, D. M., Jandacek, R. J., & McNamara, R. K. (2017). Polyunsaturated fatty acids and recurrent mood disorders: Phenomenology, mechanisms, and clinical application. *Progress in Lipid Research*, *66*, 1–13. https://doi.org/10.1016/j.plipres.2017.01.001

Middleton, P., Gomersall, J. C., Gould, J. F., Shepherd, E., Olsen, S. F., & Makrides, M. (2019). Omega-3 Fatty Acid Addition during Pregnancy. *Obstetrical and Gynecological Survey*, *74*(4), 189–191. https://doi.org/10.1097/01.ogx.0000554434.11750.dc

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, *16*(1), 22–34. https://doi.org/10.1038/nri.2015.5

Miller, E. K., & Cohen, J. D. (2001). An Integrative Theory of Prefrontal Cortex Function. *Annual Review of Neuroscience*, *24*(1), 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Milte, C. M., Parletta, N., Buckley, J. D., Coates, A. M., Young, R. M., & Howe, P. R. C. (2012). Eicosapentaenoic and docosahexaenoic acids, cognition, and behavior in children with attention-deficit/hyperactivity disorder: A randomized controlled trial. *Nutrition*, *28*(6), 670–677. https://doi.org/10.1016/j.nut.2011.12.009

Miranda, M., Morici, J. F., Zanoni, M. B., & Bekinschtein, P. (2019). Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Frontiers in Cellular Neuroscience*, *13*. https://doi.org/10.3389/fncel.2019.00363

Mocking, R. J. T., Harmsen, I., Assies, J., Koeter, M. W. J., Ruhé, H. G., & Schene, A. H. (2016). Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Translational Psychiatry*, *6*(3). https://doi.org/10.1038/tp.2016.29

Moffitt, T. E., Caspi, A., Taylor, A., Kokaua, J., Milne, B. J., Polanczyk, G., & Poulton, R. (2010). How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *Psychological Medicine*, *40*(6), 899–909. https://doi.org/10.1017/S0033291709991036

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Molendijk, M. L., Bus, B. A. A., Spinhoven, P., Penninx, B. W. J. H., Kenis, G., Prickaerts, J., … Elzinga, B. M. (2011). Serum levels of brain-derived neurotrophic factor in major depressive disorder: State-trait issues, clinical features and pharmacological treatment. *Molecular Psychiatry*, *16*(11), 1088–1095. https://doi.org/10.1038/mp.2010.98

Mollon, J., Knowles, E. E. M., Mathias, S. R., Gur, R., Peralta, J. M., Weiner, D. J., … Glahn, D. C. (2018). Genetic influence on cognitive development between childhood and adulthood. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-018-0277-0

Montgomery, P., Burton, J. R., Sewell, R. P., Spreckelsen, T. F., & Richardson, A. J. (2013). Low Blood Long Chain Omega-3 Fatty Acids in UK Children Are Associated with Poor Cognitive Performance and Behavior: A Cross-Sectional Analysis from the DOLAB Study. *PLoS ONE*, *8*(6). https://doi.org/10.1371/journal.pone.0066697

Morey-Nase, C., Phillips, L. J., Bryce, S., Hetrick, S., Wright, A. L., Caruana, E., & Allott, K. (2019). Subjective experiences of neurocognitive functioning in young people with major depression. *BMC Psychiatry*, *19*(1). https://doi.org/10.1186/s12888-019-2197-1

Moriguchi, T., Greiner, R. S., & Salem, N. (2000). Behavioral deficits associated with dietary induction of decreased brain docosahexaenoic acid concentration. *Journal of Neurochemistry*, *75*(6), 2563–2573.

Morris, M. C., Sacks, F., & Rosner, B. (1993). Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation*, *88*(2), 523–533. https://doi.org/10.1161/01.CIR.88.2.523

Müller, N., Myint, A. M., & Schwarz, M. J. (2009). The impact of neuroimmune dysregulation on neuroprotection and neurotoxicity in psychiatric disorders - Relation to drug treatment. *Dialogues in Clinical Neuroscience*, *11*(3), 319–332.

Munkholm, K., Paludan-Müller, A. S., & Boesen, K. (2019). Considering the methodological limitations in the evidence base of antidepressants for depression: A reanalysis of a network meta-analysis. *BMJ Open*, *9*(6). https://doi.org/10.1136/bmjopen-2018-024886

Murakami, K., Miyake, Y., Sasaki, S., Tanaka, K., & Arakawa, M. (2010). Fish and n-3 Polyunsaturated Fatty Acid Intake and Depressive Symptoms: Ryukyus Child Health Study. *PEDIATRICS*, *126*(3), e623–e630. https://doi.org/10.1542/peds.2009-3277

Naismith, S. L., Longley, W. A., Scott, E. M., & Hickie, I. B. (2007). Disability in major depression related to self-rated and objectively-measured cognitive deficits: A preliminary study. *BMC Psychiatry*, *7*. https://doi.org/10.1186/1471-244X-7-32

Natto, Z. S., Yaghmoor, W., Alshaeri, H. K., & Van Dyke, T. E. (2019). Omega-3 Fatty Acids Effects on Inflammatory Biomarkers and Lipid Profiles among Diabetic and Cardiovascular Disease Patients: A Systematic Review and Meta-Analysis. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-54535-x

Nemets, H. (2006). Omega-3 Treatment of Childhood Depression: A Controlled, Double-Blind Pilot Study. *American Journal of Psychiatry*, *163*(6), 1098. https://doi.org/10.1176/appi.ajp.163.6.1098

Neuringer, M., Connor, W. E., Lin, D. S., Barstad, L., & Luck, S. (1986). Biochemical and functional effects of prenatal and postnatal ω3 fatty acid deficiency on retina and brain in rhesus monkeys. *Proceedings of the National Academy of Sciences of the United States of America*, *83*(11), 4021–4025. https://doi.org/10.1073/pnas.83.11.4021

NICE. (2015). Depression in children and young people: identification and management. *National Institute for Health and Clinical Excellence*, *CG28*(September), 1–60.

Nordic Cochrane Centre, T. C. C. (2014). Review Manager 5 (RevMan 5). Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2014. https://doi.org/10.1111/j.1365-2486.2008.01672.x

Oddy, W. H., Hickling, S., Smith, M. A., A. O'Sullivan, T., Robinson, M., H. de Klerk, N., … R. Silburn, S. (2011). Dietary intake of omega-3 fatty acids and risk of depressive symptoms in adolescents. *Depression and Anxiety*, *28*(7), 582–588. https://doi.org/10.1002/da.20822

Olvet, D. M., Klein, D. N., & Hajcak, G. (2010). Depression symptom severity and error-related brain activity. *Psychiatry Research*, *179*(1), 30–37. https://doi.org/10.1016/j.psychres.2010.06.008

Orr, S. K., & Bazinet, R. P. (2008). The emerging role of docosahexaenoic acid in neuroinflammation. *Current Opinion in Investigational Drugs*, *9*(7), 735–743.

Osendarp, S. J. M., Baghurst, K. I., Bryan, J., Calvaresi, E., Hughes, D., Hussaini, M., … Wilson, C. (2007). Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia. *The American Journal of Clinical Nutrition*, *86*(4), 1082–1093. https://doi.org/10.1093/ajcn/86.4.1082

Ott, C. V., Bjertrup, A. J., Jensen, J. H., Ullum, H., Sjælland, R., Purdon, S. E., … Miskowiak, K. W. (2016). Screening for cognitive dysfunction in unipolar depression: Validation and evaluation of objective and subjective tools. *Journal of Affective Disorders*, *190*, 607–615. https://doi.org/10.1016/j.jad.2015.10.059

Outhoff, K. (2010). Antidepressant-induced sexual dysfunction. *SA Pharmaceutical Journal*, *77*(9), 17–21. https://doi.org/10.1521/capn.9.3.1.41616

Øyen, J., Kvestad, I., Midtbø, L. K., Graff, I. E., Hysing, M., Stormark, K. M., … Kjellevold,

M. (2018). Fatty fish intake and cognitive function: FINS-KIDS, a randomized controlled trial in preschool children. *BMC Medicine*, *16*(1). https://doi.org/10.1186/s12916-018-1020-z

Parletta, N., Cooper, P., Gent, D. N., Petkov, J., & O'Dea, K. (2013). Effects of fish oil supplementation on learning and behaviour of children from Australian Indigenous remote community schools: A randomised controlled trial. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *89*(2–3), 71–79. https://doi.org/10.1016/j.plefa.2013.05.001

Porter, R. J., Robinson, L. J., Malhi, G. S., & Gallagher, P. (2015). The neurocognitive profile of mood disorders - a review of the evidence and methodological issues. *Bipolar Disorders*, *17*, 21–40. https://doi.org/10.1111/bdi.12342

Portillo-Reyes, V., Perez-Garcia, M., Loya-Mendez, Y., & Puente, A. E. (2014). Clinical significance of neuropsychological improvement after supplementation with omega-3 in 8-12 years old malnourished Mexican children: A randomized, double-blind, placebo and treatment clinical trial. *Research in Developmental Disabilities*, *35*(4), 861–870.

Pottala, J. V., Talley, J. A., Churchill, S. W., Lynch, D. A., von Schacky, C., & Harris, W. S. (2012). Red blood cell fatty acids are associated with depression in a case-control study of adolescents. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *86*(4–5), 161–165. https://doi.org/10.1016/j.plefa.2012.03.002

Pottala, J. V., Yaffe, K., Robinson, J. G., Espeland, M. A., Wallace, R., & Harris, W. S. (2014). Higher RBC EPA 1 DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI Study. *Neurology*, *82*(5), 435–442. https://doi.org/10.1212/WNL.0000000000000080

Potvin, S., Charbonneau, G., Juster, R. P., Purdon, S., & Tourjman, S. V. (2016). Self-evaluation and objective assessment of cognition in major depression and attention deficit disorder: Implications for clinical practice. *Comprehensive Psychiatry*, *70*, 53–64. https://doi.org/10.1016/j.comppsych.2016.06.004

Poznanski, E., & Mokros, H. (1996). *Children's Depression Rating Scale–Revised*. *Psychopathology Bulletin* (Vol. 12). Los Angeles: WPS.

Prado, C. E., Watt, S., & Crowe, S. F. (2018). A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychology Review*, *28*(1), 32–72. https://doi.org/10.1007/s11065-018-9369-5

Psota, T. L., Gebauer, S. K., & Kris-Etherton, P. (2006). Dietary Omega-3 Fatty Acid Intake and Cardiovascular Risk. *American Journal of Cardiology*, *98*(4 SUPPL. 1), 3–18. https://doi.org/10.1016/j.amjcard.2005.12.022

Qawasmi, A., Landeros-Weisenberger, A., Leckman, J. F., & Bloch, M. H. (2012). Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. *Pediatrics*, *129*(6), 1141–1149. https://doi.org/10.1542/peds.2011-2127

Rahmawaty, S., Charlton, K., Lyons-Wall, P., & Meyer, B. J. (2017). Development and validation of a food frequency questionnaire to assess omega-3 long chain polyunsaturated fatty acid intake in Australian children aged 9–13 years. *Journal of Human Nutrition and Dietetics*, *30*(4), 429–438. https://doi.org/10.1111/jhn.12439

Ramakrishnan, U., Imhoff-Kunsch, B., & Digirolamo, A. M. (2009). Role of docosahexaenoic acid in maternal and child mental health. *American Journal of Clinical Nutrition*, *89*(3). https://doi.org/10.3945/ajcn.2008.26692F

Rapaport, M. H., Nierenberg, A. A., Schettler, P. J., Kinkead, B., Cardoos, A., Walker, R., & Mischoulon, D. (2016). Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: A proof-of-concept study. *Molecular Psychiatry*, *21*(1), 71–79. https://doi.org/10.1038/mp.2015.22

Richardson, A. J., Burton, J. R., Sewell, R. P., Spreckelsen, T. F., & Montgomery, P. (2012). Docosahexaenoic Acid for Reading, Cognition and Behavior in Children Aged 7-9 Years: A Randomized, Controlled Trial (The DOLAB Study). *PLoS ONE*, *7*(9). https://doi.org/10.1371/journal.pone.0043909

Richardson, A. J., & Montgomery, P. (2005). The Oxford-Durham Study: A Randomized, Controlled Trial of Dietary Supplementation With Fatty Acids in Children With Developmental Coordination Disorder. *Pediatrics*, *115*(5), 1360–1366. https://doi.org/10.1542/peds.2004-2164

Riemer, S., Maes, M., Christophe, A., & Rief, W. (2010). Lowered ω-3 PUFAs are related to major depression, but not to somatization syndrome. *Journal of Affective Disorders*, *123*(1–3), 173–180. https://doi.org/10.1016/j.jad.2009.08.004

Robson, L. G., Dyall, S., Sidloff, D., & Michael-Titus, A. T. (2010). Omega-3 polyunsaturated fatty acids increase the neurite outgrowth of rat sensory neurones throughout development and in aged animals. *Neurobiology of Aging*, *31*(4), 678–687. https://doi.org/10.1016/j.neurobiolaging.2008.05.027

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029–2040. https://doi.org/10.1017/S0033291713002535

Rogers, P. J., Appleton, K. M., Kessler, D., Peters, T. J., Gunnell, D., Hayward, R. C., … Ness, A. R. (2008). No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. *British Journal of Nutrition*, *99*(2), 421–431. https://doi.org/10.1017/S0007114507801097

Rosenblat, J. D., Cha, D. S., Mansur, R. B., & McIntyre, R. S. (2014). Inflamed moods: A review of the interactions between inflammation and mood disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *53*, 23–34. https://doi.org/10.1016/j.pnpbp.2014.01.013

Rosenblat, J. D., Kakar, R., & McIntyre, R. S. (2015). The Cognitive Effects of Antidepressants in Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *The International Journal of Neuropsychopharmacology*, *19*(2). https://doi.org/10.1093/ijnp/pyv082

Rücker, G., Cates, C. J., & Schwarzer, G. (2017). Methods for including information from multi-arm trials in pairwise meta-analysis. *Research Synthesis Methods*, *8*(4), 392–403. https://doi.org/10.1002/jrsm.1259

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2008). Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *Focus*, *6*(1), 128–142. https://doi.org/10.1176/foc.6.1.foc128

Russell, F. D., & Bürgin-Maunder, C. S. (2012). Distinguishing health benefits of eicosapentaenoic and docosahexaenoic acids. *Marine Drugs*, *10*(11), 2535–2559. https://doi.org/10.3390/md10112535

Ryan, A. S., & Nelson, E. B. (2008). Assessing the effect of docosahexaenoic acid on cognitive functions in healthy, preschool children: A randomized, placebo-controlled, double-blind study. *Clinical Pediatrics*, *47*(4), 355–362. https://doi.org/10.1177/0009922807311730

Sachs-Ericsson, N., Joiner, T., & Blazer, D. G. (2008). The influence of lifetime depression on self-reported memory and cognitive problems: Results from the National Comorbidity Survey - Replication. *Aging and Mental Health*, *12*(2), 183–192. https://doi.org/10.1080/13607860801951739

Salem, N., Litman, B., Kim, H. Y., & Gawrisch, K. (2001). Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids*, *36*(9), 945–959. https://doi.org/10.1007/s11745-001-0805-6

Samieri, C., Féart, C., Proust-Lima, C., Peuchant, E., Dartigues, J.-F., Amieva, H., & Barberger-Gateau, P. (2011). Omega-3 fatty acids and cognitive decline: modulation by ApoEε4 allele and depression. *Neurobiology of Aging*, *32*(12), 2317.e13-2317.e22. https://doi.org/10.1016/j.neurobiolaging.2010.03.020

Samieri, C., Maillard, P., Crivello, F., Proust-Lima, C., Peuchant, E., Helmer, C., … Barberger-Gateau, P. (2012). Plasma long-chain omega-3 fatty acids and atrophy of the medial temporal lobe. *Neurology*, *79*(7), 642–650. https://doi.org/10.1212/WNL.0b013e318264e394

Samson, R. D., & Barnes, C. A. (2013). Impact of aging brain circuits on cognition. *European Journal of Neuroscience*, *37*(12), 1903–1915. https://doi.org/10.1111/ejn.12183

Sanchez-Villegas, A., Henríquez, P., Figueiras, A., Ortuño, F., Lahortiga, F., & Martínez-González, M. A. (2007). Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. *European Journal of Nutrition*, *46*(6), 337–346. https://doi.org/10.1007/s00394-007-0671-x

Schmaal, L., Veltman, D. J., Van Erp, T. G. M., Smann, P. G., Frodl, T., Jahanshad, N., … Hibar, D. P. (2016). Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA Major Depressive Disorder working group. *Molecular Psychiatry*, *21*(6), 806–812. https://doi.org/10.1038/mp.2015.69

Schmaal, L., Yücel, M., Ellis, R., Vijayakumar, N., Simmons, J. G., Allen, N. B., & Whittle, S. (2017). Brain Structural Signatures of Adolescent Depressive Symptom Trajectories: A Longitudinal Magnetic Resonance Imaging Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(7), 593-601.e9.

https://doi.org/10.1016/j.jaac.2017.05.008

Schmidt, M. (1996a). *Auditory and Verbal Learning Test. A handbook*. Los Angeles: Western Psychological Association.

Schmidt, M. (1996b). *Rey Auditory and Verbal Learning Test. A handbook*. Los Angeles, CA: Western Psychological Services.

Scott, D. T., Janowsky, J. S., Carroll, R. E., Taylor, J. A., Auestad, N., & Montalto, M. B. (1998). Formula Supplementation With Long-chain Polyunsaturated Fatty Acids: Are There Developmental Benefits? *Pediatrics*, *102*(5), e59–e59. https://doi.org/10.1542/peds.102.5.e59

Scott, E. G., Luxmore, B., Alexander, H., Fenn, R. L., & Christopher, N. C. (2006). Screening for Adolescent Depression in a Pediatric Emergency Department. *Academic Emergency Medicine*, *13*(5), 537–542. https://doi.org/10.1111/j.1553-2712.2006.tb01005.x

Semkovska, M., Quinlivan, L., O'Grady, T., Johnson, R., Collins, A., O'Connor, J., … Gload, T. (2019). Cognitive function following a major depressive episode: a systematic review and meta-analysis. *The Lancet Psychiatry*, *6*(10), 851–861. https://doi.org/10.1016/S2215-0366(19)30291-3

Sergeant, S., Rahbar, E., & Chilton, F. H. (2016). Gamma-linolenic acid, Dihommo-gamma linolenic, Eicosanoids and Inflammatory Processes. *European Journal of Pharmacology*, *785*, 77–86. https://doi.org/10.1016/j.ejphar.2016.04.020

Serini, S., Bizzarro, A., Piccioni, E., Fasano, E., Rossi, C., Lauria, A., … Calviello, G. (2012). EPA and DHA Differentially Affect In Vitro Inflammatory Cytokine Release by Peripheral Blood Mononuclear Cells from Alzheimer's Patients. *Current Alzheimer Research*, *9*(8), 913–923. https://doi.org/10.2174/156720512803251147

Serretti, A., & Porcelli, S. (2018). Antidepressant induced weight gain. *BMJ*, k2151. https://doi.org/10.1136/bmj.k2151

Shaikh, S. R., & Teague, H. (2012). N-3 fatty acids and membrane microdomains: From model membranes to lymphocyte function. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *87*(6), 205–208. https://doi.org/10.1016/j.plefa.2012.09.007

Sharma, T., Guski, L. S., Freund, N., & Gøtzsche, P. C. (2016). Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ*, i65. https://doi.org/10.1136/bmj.i65

Shilyansky, C., Williams, L. M., Gyurak, A., Harris, A., Usherwood, T., & Etkin, A. (2016). Effect of antidepressant treatment on cognitive impairments associated with depression: A randomised longitudinal study. *The Lancet Psychiatry*, *3*(5), 425–435. https://doi.org/10.1016/S2215-0366(16)00012-2

Shokri-Kojori, E., Tomasi, D., Wiers, C. E., Wang, G. J., & Volkow, N. D. (2017). Alcohol affects brain functional connectivity and its coupling with behavior: Greater effects in male heavy drinkers. *Molecular Psychiatry*, *22*(8), 1185–1195. https://doi.org/10.1038/mp.2016.25

Shulkin, M., Pimpin, L., Bellinger, D., Kranz, S., Fawzi, W., Duggan, C., & Mozaffarian, D. (2018). N-3 fatty acid supplementation in mothers, preterm infants, and term infants and childhood psychomotor and visual development: A systematic review and meta-analysis. *Journal of Nutrition*, *148*(3), 409–418. https://doi.org/10.1093/jn/nxx031

Simmer, K. (1998). Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd000375

Simopoulos, A. P. (2002). Omega-3 fatty acids in inflammation and autoimmune diseases. *Journal of the American College of Nutrition*, *21*(6), 495–505. https://doi.org/10.1080/07315724.2002.10719248

Simopoulos, A. P. (2008). The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases. *Experimental Biology and Medicine*, *233*(6), 674–688. https://doi.org/10.3181/0711-MR-311

Simopoulos, A. P. (2011a). Evolutionary Aspects of Diet: The Omega-6/Omega-3 Ratio and the Brain. *Molecular Neurobiology*, *44*(2), 203–215. https://doi.org/10.1007/s12035-010-8162-0

Simopoulos, A. P. (2011b). Omega-3 fatty acids in health and disease and in growth and development. *The American Journal of Clinical Nutrition*, *54*(3), 438–463. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1908631

Sinn, N., Bryan, J., & Wilson, C. (2008). Cognitive effects of polyunsaturated fatty acids in children with attention deficit hyperactivity disorder symptoms: A randomised controlled trial. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *78*(4–5), 311–326. https://doi.org/10.1016/j.plefa.2008.04.004

Skandali, N., Rowe, J. B., Voon, V., Deakin, J. B., Cardinal, R. N., Cormack, F., … Sahakian, B. J. (2018). Dissociable effects of acute SSRI (escitalopram) on executive, learning and emotional functions in healthy humans. *Neuropsychopharmacology*, *43*(13), 2645–2651. https://doi.org/10.1038/s41386-018-0229-z

Smith, C. (2009). Mental health of children and young people in hospital. *Paediatric Nursing*, *21*(5), 28–31. https://doi.org/10.7748/paed2009.06.21.5.28.c7079

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin*, *139*(1), 81–132. https://doi.org/10.1037/a0028727

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, *6*(3), 309–315. https://doi.org/10.1038/nn1008

Spitzer, S., Weber, D., & Lutz, W. (2019). *Who is telling the truth ? Biases in self-reported physical and cognitive health status of older Europeans Approved by :*

Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*, *99*(2), 195–231. https://doi.org/10.1037//0033-295x.99.2.195

Srisurapanont, M., Suttajit, S., Eurviriyanukul, K., & Varnado, P. (2017). Discrepancy between objective and subjective cognition in adults with major depressive disorder. *Scientific Reports*, *7*(1). https://doi.org/10.1038/s41598-017-04353-w

Sterne, J., Egger, M., & Moher, D. (editors). (2006). Chapter 10: Addressing reporting biases. In J. P. T. Higgins & S. Green (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Retrieved from www.handbook.cochrane.org

Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstad, N., Mahon, A., … Burgess, J. R. (2003). EFA Supplementation in Children with Inattention, Hyperactivity, and other Disruptive Behaviors. *Lipids*, *38*(10), 1007–1021. https://doi.org/10.1007/s11745-006-1155-0

Sublette, M. E., Ellis, S. P., Geant, A. L., & Mann, J. J. (2011). Meta-analysis of the effects of Eicosapentaenoic Acid (EPA) in clinical trials in depression. *Journal of Clinical Psychiatry*, *72*(12), 1577–1584. https://doi.org/10.4088/JCP.10m06634

Sublette, M. E., Segal-Isaacson, C. J., Cooper, T. B., Fekri, S., Vanegas, N., Galfalvy, H. C., … Mann, J. J. (2011). Validation of a Food Frequency Questionnaire to Assess Intake of n-3 Polyunsaturated Fatty Acids in Subjects with and without Major Depressive Disorder. *Journal of the American Dietetic Association*, *111*(1). https://doi.org/10.1016/j.jada.2010.10.007

Sun, G. Y., Simonyi, A., Fritsche, K. L., Chuang, D. Y., Hannink, M., Gu, Z., … Beversdorf, D. Q. (2018). Docosahexaenoic acid (DHA): An essential nutrient and a nutraceutical for brain health and diseases. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *136*, 3–13. https://doi.org/10.1016/j.plefa.2017.03.006

Sunderland, A., Harris, J. E., & Baddeley, A. D. (1983). Do laboratory tests predict everyday memory? A neuropsychological study. *Journal of Verbal Learning and Verbal Behavior*, *22*(3), 341–357. https://doi.org/10.1016/S0022-5371(83)90229-3

Svendsen, A. M., Kessing, L. V., Munkholm, K., Vinberg, M., & Miskowiak, K. W. (2012). Is there an association between subjective and objective measures of cognitive function in patients with affective disorders? *Nordic Journal of Psychiatry*, *66*(4), 248–253. https://doi.org/10.3109/08039488.2011.626870

Takeuchi, T., Fukumoto, Y., & Harada, E. (2002). Influence of a dietary n-3 fatty acid deficiency on the cerebral catecholamine contents, EEG and learning ability in rat. *Behavioural Brain Research*, *131*(1–2), 193–203. https://doi.org/10.1016/S0166-4328(01)00392-8

Tannous, J., Godlewska, B. R., Tirumalaraju, V., Soares, J. C., Cowen, P. J., & Selvaraj, S. (2020). Stress, inflammation and hippocampal subfields in depression: A 7 Tesla MRI Study. *Translational Psychiatry*, *10*(1). https://doi.org/10.1038/s41398-020-0759-0

Tanskanen, A. (2001). Fish Consumption, Depression, and Suicidality in a General Population. *Archives of General Psychiatry*, *58*(5), 512–513. https://doi.org/10.1001/archpsyc.58.5.512

Tapp, Z. M., Godbout, J. P., & Kokiko-Cochran, O. N. (2019). A Tilted Axis: Maladaptive

Inflammation and HPA Axis Dysfunction Contribute to Consequences of TBI. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00345

Thapar, A., Collishaw, S., Potter, R., & Thapar, A. K. (2010). Managing and preventing depression in adolescents. *BMJ (Online)*, *340*(7740), 254–258. https://doi.org/10.1136/bmj.c209

Thompson, P. M., Gledd, J. N., Woods, R. P., MacDonald, D., Evans, A. C., & Toga, A. W. (2000). Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature*, *404*(6774), 190–193. https://doi.org/10.1038/35004593

Timonen, M. (2004). Fish consumption and depression: the Northern Finland 1966 birth cohort study. *Journal of Affective Disorders*, *82*(3), 447–452. https://doi.org/10.1016/j.jad.2004.02.002

Trivedi, J. (2006). Cognitive deficits in psychiatric disorders: Current status. *Indian Journal of Psychiatry*, *48*(1), 10. https://doi.org/10.4103/0019-5545.31613

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience*, *10*(6), 397–409. https://doi.org/10.1038/nrn2647

Vaisman, N., Kaysar, N., Zaruk-Adasha, Y., Pelled, D., Brichon, G., Zwingelstein, G., & Bodennec, J. (2008). Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: Effect of dietary n-3 fatty acids containing phospholipids. *American Journal of Clinical Nutrition*, *87*(5), 1170–1180. https://doi.org/87/5/1170 [pii]

Van Der Merwe, L. F., Moore, S. E., Fulford, A. J., Halliday, K. E., Drammeh, S., & Young, S. (2013). Long-chain PUFA supplementation in rural African infants: A randomized controlled trial of effects on gut integrity, growth, and cognitive development. *American Journal of Clinical Nutrition*, *97*(1), 45–57. https://doi.org/http://dx.doi.org/10.3945/ajcn.112.042267

van der Wurff, I. S. M., Meyer, B. J., & de Groot, R. H. M. (2020). Effect of omega-3 long chain polyunsaturated fatty acids (N-3 LCPUFA) supplementation on cognition in children and adolescents: A systematic literature review with a focus on n-3 LCPUFA blood values and dose of DHA and EPA. *Nutrients*, *12*(10), 1–28. https://doi.org/10.3390/nu12103115

van der Wurff, I. S. M., Von Schacky, C., Berge, K., Zeegers, M. P., Kirschner, P. A., Groot, D., & H, R. (2016). Association between Blood Omega-3 Index and Cognition in Typically Developing Dutch Adolescents. *Nutrients*, *8*(1).

van der Wurff, I. S. M., von Schacky, C., Bergeland, T., Leontjevas, R., Zeegers, M. P., Kirschner, P. A., & de Groot, R. H. M. (2019). Exploring the association between whole blood Omega-3 Index, DHA, EPA, DHA, AA and n-6 DPA, and depression and self-esteem in adolescents of lower general secondary education. *European Journal of Nutrition*, *58*(4), 1429–1439. https://doi.org/10.1007/s00394-018-1667-4

Vaughan, V. C., Hassing, M. R., & Lewandowski, P. A. (2013). Marine polyunsaturated fatty acids and cancer therapy. *British Journal of Cancer*, *108*(3), 486–492.

https://doi.org/10.1038/bjc.2012.586

Vesco, A. T., Young, A. S., Arnold, L. E., & Fristad, M. A. (2018). Omega-3 supplementation associated with improved parent-rated executive function in youth with mood disorders: secondary analyses of the omega 3 and therapy (OATS) trials. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *59*(6), 628–636. https://doi.org/10.1111/jcpp.12830

Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: A meta-analysis of MRI studies. *American Journal of Psychiatry*, *161*(11), 1957–1966. https://doi.org/10.1176/appi.ajp.161.11.1957

Vilgis, V., Silk, T. J., & Vance, A. (2015). Executive function and attention in children and adolescents with depressive disorders: a systematic review. *European Child and Adolescent Psychiatry*, *24*(4), 365–384. https://doi.org/10.1007/s00787-015-0675-7

Voigt, R. G., Llorente, A. M., Jensen, C. L., Fraley, J. K., Berretta, M. C., & Heird, W. C. (2001). A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *Journal of Pediatrics*, *139*(2), 189–196. https://doi.org/10.1067/mpd.2001.116050

von Schacky, C. (2016). ω-3-Fettsäuren und Hirnfunktion. *Zeitschrift Für Orthomolekulare Medizin*, *2*(02), 6–14. https://doi.org/10.1055/s-0042-106429

von Schacky, C. (2019a). Confusion about the effects of omega-3 fatty acids: Contemplation of study data taking the omega-3 index into consideration. *Internist*. https://doi.org/10.1007/s00108-019-00687-x

von Schacky, C. (2019b). Verwirrung um die Wirkung von Omega-3-Fettsäuren. *Der Internist*, *60*(12), 1319–1327. https://doi.org/10.1007/s00108-019-00687-x

Von Schacky, C. (2015). Omega-3 fatty Acids in cardiovascular disease - An uphill battle. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *92*, 41–47. https://doi.org/10.1016/j.plefa.2014.05.004

von Stumm, S., & Plomin, R. (2015). Socioeconomic status and the growth of intelligence from infancy through adolescence. *Intelligence*, *48*, 30–36. https://doi.org/10.1016/j.intell.2014.10.002

Wagner, S., Doering, B., Helmreich, I., Lieb, K., & Tadić, A. (2012). A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. *Acta Psychiatrica Scandinavica*, *125*(4), 281–292. https://doi.org/10.1111/j.1600-0447.2011.01762.x

Wagner, S., Müller, C., Helmreich, I., Huss, M., & Tadić, A. (2014). A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *European Child and Adolescent Psychiatry*, *24*(1), 5–19. https://doi.org/10.1007/s00787-014-0559-2

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children - Fourth Edition*. San Antonio: TX: The Psychological Corporation.

Weiser, M., Butt, C., & Mohajeri, M. (2016). Docosahexaenoic acid and cognition throughout the lifespan. *Nutrients*, *8*(2). https://doi.org/10.3390/nu8020099

Wen, D. J., Poh, J. S., Ni, S. N., Chong, Y.-S., Chen, H., Kwek, K., … Meaney, M. J. (2017). Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. *Translational Psychiatry*, *7*(4), e1103. https://doi.org/10.1111/j.1600-0447.2012.01897.x

Werkman, S. H., & Carlson, S. E. (1996). A randomized trial of visual attention of preterm infants fed docosahexaenoic acid until nine months. *Lipids*, *31*(1), 91–97.

Widenhorn-Müller, K., Schwanda, S., Scholz, E., Spitzer, M., & Bode, H. (2014). Effect of supplementation with long-chain ω-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): A randomized placebo-controlled intervention trial. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *91*(1–2), 49–60.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., … Steinhausen, H.-C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(9), 655–679. https://doi.org/10.1016/j.euroneuro.2011.07.018

Wittchen, H. U., Nelson, C. B., & Lachner, G. (1998). Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. *Psychological Medicine*, *28*(1), 109–126. https://doi.org/10.1017/S0033291797005928

World Health Organization. (2017). Depression and other common mental disorders: global health estimates (pp. 1–24). https://doi.org/CC BY-NC-SA 3.0 IGO

World Health Organization. (2018). *International classification of diseases for mortality and morbidity statistics (11th Revision)*.

Young, J. J., Bruno, D., & Pomara, N. (2014). A review of the relationship between proinflammatory cytokines and major depressive disorder. *Journal of Affective Disorders*, *169*, 15–20. https://doi.org/10.1016/j.jad.2014.07.032

Yurko-Mauro, K., Alexander, D. D., & Van Elswyk, M. E. (2015). Docosahexaenoic acid and adult memory: A systematic review and meta-analysis. *PLoS ONE*, *10*(3). https://doi.org/10.1371/journal.pone.0120391

Zhang, L., Liu, H., Kuang, L., Meng, H., & Zhou, X. (2019). Omega-3 fatty acids for the treatment of depressive disorders in children and adolescents: A meta-analysis of randomized placebo-controlled trials. *Child and Adolescent Psychiatry and Mental Health*, *13*(1). https://doi.org/10.1186/s13034-019-0296-x

Zimmer, L., Delion-Vancassel, S., Durand, G., Guilloteau, D., Bodard, S., Besnard, J. C., & Chalon, S. (2000). Modification of dopamine neurotransmission in the nucleus accumbens of rats deficient in n-3 polyunsaturated fatty acids. *Journal of Lipid Research*, *41*(1), 32–40.

Zisook, S., Lesser, I., Stewart, J. W., Wisniewski, S. R., Balasubramani, G. K., Fava, M., … Rush, A. J. (2007). Effect of age at onset on the course of major depressive disorder.

American Journal of Psychiatry, *164*(10), 1539–1546. https://doi.org/10.1176/appi.ajp.2007.06101757

Zuckerman, H., Pan, Z., Park, C., Brietzke, E., Musial, N., Shariq, A. S., … McIntyre, R. S. (2018). Recognition and Treatment of Cognitive Dysfunction in Major Depressive Disorder. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00655

Acknowledgements

I would like to express my sincerest gratitude to everyone who supported me throughout this journey of successfully acquiring my PhD. Although the list is presumably endless, I'd like to specifically point out and thank the following people:

First and foremost, I would like to express my thanks to PD Dr. med. Gregor Berger and Prof. Dr. med. Dipl.- Psych. Susanne Walitza for giving me the opportunity to participate in this most significant clinical trial. Throughout the study, I was allocated great responsibility and given a lot of trust, which I am very appreciative of. I would also like to thank both for strongly supporting me in my pursuit of a dual career by letting me be part of the emergency services and making it possible for me to start my clinical training. I am very grateful for this opportunity and appreciate that it shows a lot of belief in my capabilities. Thank you, Gregor, also for your great sense of humor and your immeasurable enthusiasm related to the clinical trial.

Most importantly, I would like to thank my supervisor Prof. Dr. Renate Drechsler for providing guidance and feedback throughout the entire process in a most sympathetic and compassionate way. I am especially grateful to her for always making me feel confident about my abilities and motivating me even in difficult stages of my PhD. Furthermore, I would like to thank Prof. Dr. rer. nat. Lutz Jäncke not only for agreeing to supervise my PhD thesis and being part of the doctoral committee, but especially for igniting the spark for my interest in neuropsychological research to begin with.

I am especially thankful for the support I have received from our study coordinator and post-doctoral researcher Dr. Isabelle Häberling throughout the entire process of my PhD. Isabelle inspired me both as a scientist but equally as a human being and I would like to express my deepest gratitude for her selfless and appreciative guidance. Another key individual throughout my journey I would like to thank is my fellow PhD student Dr. Noemi Baumgartner, a great colleague but an even better friend. Thank you for being there for me no matter what day or time. Thank you also to my other fellow PhD students Mona Albermann and Michael Strumberger for many hours of laughter and the most amiable collaboration throughout.

Needless to say, I would never have been able to successfully complete my PhD thesis without the countless hours patients and parents participating in the clinical trial spent in clinical interviews and cognitive assessments. Despite suffering from a debilitating psychiatric disease, patients donated their valuable time to the clinical trial which I am most impressed and appreciative of. Thank you also to all investigators and clinicians at KJPP Zurich, UPK Basel, Clienia

Littenheid AG, Klinik Sonnenhof, KJPD Thurgau and St. Gallen for their help with recruiting patients for the study.
Lastly, thank you to my family, my friends and most importantly my partner David for supporting me and excusing my slightly off-key behavior in stressful times.

Funding

This dissertation is funded by the Swiss National Science Foundation.

Curriculum Vitae

PERSONAL DETAILS

Name: Sophie Emery

Date of birth: 5 June 1992

Nationalities: Swiss, Finnish

EDUCATION

January 2020 – present	Training in cognitive behavioral and systemic psychotherapy at the **Institut für Psychotherapie des Kindes- und Jugendalters der Universitätskliniken Basel, Bern, Zürich" (IPKJ)**
August 2017 – present	**University of Zurich CH**, PhD student in Psychology Matriculation date: 01 November 2017 Thesis: "Omega-3 and cognition: The influence of omega-3 fatty acids on cognitive functions in youths." Main supervisor: Prof. Dr. rer. nat. Lutz Jäncke Second supervisor: Prof. Dr. phil. Renate Drechsler
2015 – 2017	**University of Zurich CH**, MSc in Psychology Emphasis: Cognitive psychology and cognitive neurosciences Thesis: "Experience dependent music processing in the brain; using fICA to identify the brain networks involved" Supervisor: Prof. Dr. rer. nat. Lutz Jäncke
2011 – 2014	**University of Zurich CH**, BSc in Psychology Minor: Journalism and Communication Sciences Thesis: „Das Gehirn als komplexes Netzwerk - das strukturelle Konnektom und dessen Anwendung in der Schizophrenieforschung" Supervisor: Dr. Franziskus Liem

EMPLOYMENT HISTORY

April 2020 – current	**KJPP Zurich** Postgraduate psychologist 20-30% KANT emergency services Supervisor: PD. Dr. med. Gregor Berger Address: Neumünsterallee 9, 8032 Zürich
August 2017 – current	**KJPP Zurich** PhD student 60% Project manager: PD Dr. med. Gregor Berger Address: Neumünsterallee 9, 8032 Zürich
January 2015 – July 2017	**profawo Zürich** Commercial assistant 40% - 60% Supervisor: Maurizio Nuzzo Address: Zähringerstrasse 26, 8001 Zürich
August 2014 – October 2014	**Psychiatric University Hospital Zurich (PUK)** Intern 100%, “Psychologischer Dienst” Supervisor: Dr. phil. Elena Hofmann Address: Lenggstrasse 31, 8032 Zürich
February 2013 – June 2014	**University of Zurich** Tutor at the department of Clinical Psychology and Psychotherapy Supervisor: Prof. Dr. Ulrike Ehlert Address: Rämistrasse 71, 8006 Zürich

SUPERVISION OF STUDENTS/JUNIOR RESEARCHERS

August 2019 - June 2020	Supervision of Master's thesis Title: Gedächtnisleistung depressiver Jugendlicher und der Zusammenhang mit Omega-3 Fettsäuren Main supervisor: Prof. Dr. phil. Renate Drechsler

TEACHING ACTIVITIES

February 2013 – June 2014	**University of Zurich** Tutor at the department of Clinical Psychology and Psychotherapy

PUBLICATIONS

2020

Emery, S., Häberling, I., Berger, G., Walitza, S., Schmeck, K., Albert, T., … Drechsler, R. (2020). Omega-3 and its domain-specific effects on cognitive test performance in youths: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, 112, 420–436. https://doi.org/10.1016/j.neubiorev.2020.02.016

Emery, S., Häberling, I., Berger, G., Baumgartner, N., Strumberger, M., Albermann, M., … Drechsler, R. (2020). Verbal Memory Performance in Depressed Children and Adolescents: Associations with EPA but Not DHA and Depression Severity. *Nutrients, 12*(12), 3630. https://doi.org/10.3390/nu12123630

Baumgartner, N., Häberling, I., **Emery, S**., Strumberger, M., Nalani, K., Erb, S., … Berger, G. (2020). When parents and children disagree: Informant discrepancies in reports of depressive symptoms in clinical interviews. *Journal of Affective Disorders*, 272, 223–230. https://doi.org/10.1016/j.jad.2020.04.008

Baumgartner, N., Foster, S., **Emery S**., Berger, G., Walitza, S., Häberling, I., (2020). How are discrepant parent-child reports integrated? A case of depressed adolescents. Manuscript submitted for publication.

2019

Häberling, I., Baumgartner, N., **Emery, S**., Keller, P., Strumberger, M., Nalani, K., … Berger, G. (2019). Anxious depression as a clinically relevant subtype of pediatric major depressive disorder. *Journal of Neural Transmission*, 126(9), 1217–1230. https://doi.org/10.1007/s00702-019-02069-x

Baumgartner, N., Berger, G., **Emery S**., Strumberger, M., Nalani, K., Wöckel, L., … Häberling, I., (2019). Characterizing depressed adolescents with borderline features: clinical and psychopathological profile. Manuscript submitted for publication.

CONFERENCE CONTRIBUTIONS

2020

Gesellschaft für Neuropsychologie (GNP), online conference: Poster: "Omega-3 Fettsäuren und kognitive Testleistung: Supplementierungseffekte im Jugendalter - eine Meta-Analyse", September 2020

European Society for Child and Adolescent Psychiatry (ESCAP) research academy meeting, Zurich, Switzerland (videoconference): Oral contribution "Current evidence for beneficial supplementation effects of omega-3 fatty acids on cognitive test performance in youths", August 2020

Schweizerische Gesellschaft für Kinder- und Jugendpsychiatrie und -psychotherapie (SGKJPP), Zurich, Switzerland: Poster "Is there evidence for a beneficial effect of omega-3 supplementation on cognitive test performance in youths? - Results of a meta-analysis", August 2020

2019

Federation of the European Societies of Neuropsychology (FESN), Milan, Italy: Poster «Association between executive dysfunction in everyday life and severity of depression symptoms in children and adolescents with major depression», September 2019

Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie e. V. (DGKJP), Mannheim, Germany: Poster «Beeinträchtigung exekutiver Funktionen im Alltag bei depressiven Kindern und Jugendlichen erfasst mit dem Verhaltensinventar zur Beurteilung exekutiver Funktionen (BRIEF)», April 2019

2018

Burghölzli Meeting, Zurich, Switzerland: Poster «Executive functions in depressed children and adolescents. Behaviour Rating Inventory of Executive Function (BRIEF) profiles in depressed and healthy subjects", October 2018

PERSONAL SKILLS

Language skills

German: Native speaker

English: Excellent command (International Baccalaureate)

French: Very good command

Swedish: Native speaker

Italian: Basic communication skills

Finnish: Basic communication skills

Digital competence

Microsoft Office

R (basic user)

SPSS (independent user)

RevMan (independent user)

EEG (19-Kanal Medic 23 System (BEE Medic GmbH))